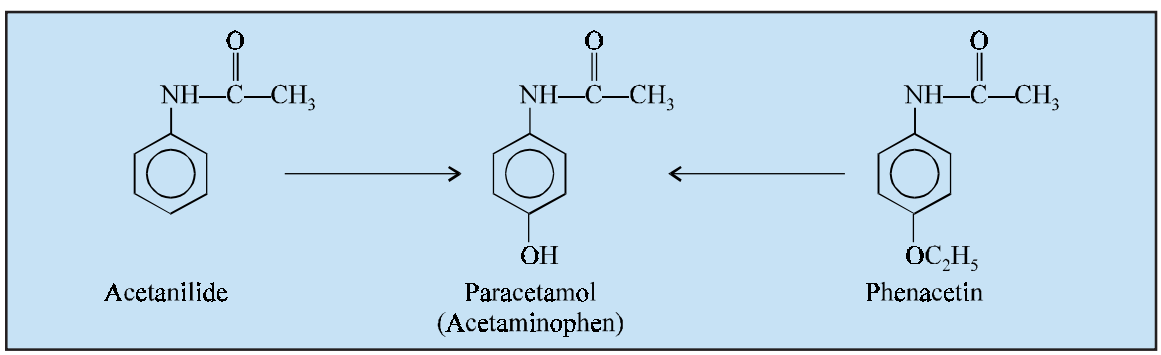
Chapter

10 Antipyretic Analgesics

1. INTRODUCTION

Antipyretic analgesics or **febrifuges** are remedial agents that lower the temperature of the body in pyrexia *i.e.,* in situations when the body temperatures has been raised above normal. In therapeutic doses they do not have any effect on normal body temperature. They exert their action on the heat regulating centre in the hypothalamus. These antipyretic agents also have mild analgesic activity. Amongst the most common group of compounds used as antipyretic analgesics are salicylates, aniline and aminophenol analogues, pyrazolones and quinoline derivatives. Though these heterogenous groups of compounds are analgesics, they have no addictive properties. Their analgesic use is limited to mild aches and pains like headache and backache.

Alternatively, **'antipyretic'** is the terminology quite frequently applied to drugs which essentially help to reduce fever to normal body temperature (*i.e.,* 98.4°F or 37°C). It is, however, worthwhile to mention here that the **'drug substances'** belonging to this particular category usually possess the ability to alleviate the sensation of pain threshold ranging from mild to severe status. These antipyretic agents are also found to be significantly effective in reducing fever to normal levels in humans. The '*drugs*' that are most commonly included here are, namely : acetanilide ; phenacetin (acetophentidin) ; and **paracetamol** [**acetaminophen** (known in US), *para*-acetaminophenol]. Interestingly, the aforesaid *three* drug entities are interrelated to one another *metabolically*, as illustrated below :



It is worthwhile to mention here that both acetanilide and phenacetin have has been withdrawn completely from being used because of its numerous toxic and undesirable effects, such as : skin

manifestations, jaundice, cardiac irregularities, and a relatively high incidence of methemoglobinemia* ; and quite seldomnly acute blood dyscrasias, for instance : hemolytic anemia. *Phenacetin* has also been dropped as a 'drug' since 1982 in US by virtue of the fact that it earned a bad reputation for causing nephrotoxicity due to its high-dose long-term abuse in several parts of the globle. It was also reported to cause kidney and liver cancer.

Paracetamol (acetaminophen) enjoys still the world-wide recognition as the only **'aniline-based analgetic-antipyretic'** for its abundant utility in controlling fever in most non-inflammatory conditions very much akin to **'aspirin'.** It has also been demonstrated adequately that both paracetamol and aspirin are **'equianalgetic'** at a dose of 650 mg.

Analgesics may be defined as–**'agents that relieve pain by elevating the pain threshold without disturbing consciousness or altering other sensory-modalities'. Besides, 'pain' may also be defined in psychological perspective as—'a particular type of sensory experience distinguished by nerve tissue from sensations, such as : touch, heat, pressure and cold'.** In the latest context '*pain*' essentially involves a major chunk of psychological factor which exclusively rests on perception. Therefore, more realistically '*pain*' may be defined introspectively in an exclusive manner.

Broadly speaking, the most probable and logical explanation for the '*mechanism*' by which certain analgesics specifically enhance the pain threshold has been caused solely due to the presence of the **'opiate receptors'** strategically located in selected parts of the CNS overtly and covertly associated with the pain regulation. It has been established that the **'opiate receptors'** are located in the following critical zones, namely :

(*a*) Medial thalamus which processes chronic, deep and burning pain that is usually suppressed by **narcotic analgesics only,**

(*b*) Brainstem's vagus nuclei which triggers the **'cough centres',** and

(*c*) Layers I and II in the spinal cord at the specific zone where the different nerves which solely hold the pain perception first synapse.

Importantly, **'endorphins'**** mostly logistically lower the intensity of pain by modulating particularly the pain threshold the critical material point at which one may commence to perceive a stimulus as **'painful'** sensation.

2. CLASSIFICATION

Antipyretic analgesics may be classified on the basis of their chemical structures.

2.1. Aniline and p-Aminophenol Analogues

In 1886, Cohn and Hepp first identified the powerful antipyretic activities residing in both aniline and acetanilid. The basic origin of this particular class of compounds from aniline has probably suggested these to be known as **'coal tar analgesics'.** However, the aminophenols (*o, m, p*) are reported to be

*The clinical condition in which more than 1% of haemoglobin in blood has been oxidized to the (Fe^{3+}) form. The principal symptom is *cyanosis.*

A generic name coined from **endogenous and **morphine** ; and commonly used for all native brain peptides having essentially the opiate-like action.

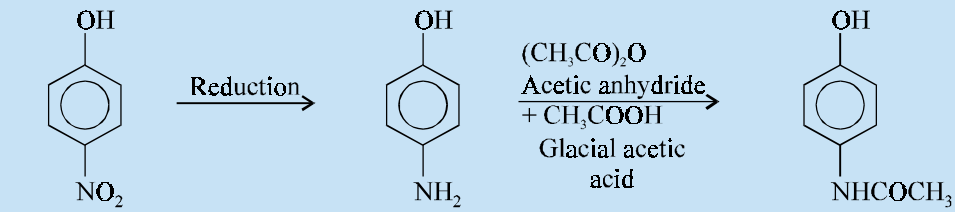
relatively less toxic than aniline. The *para*-isomer is claimed to be the least toxic of the three isomers of aminophenols and it also possesses a significant antipyretic action. A few examples belonging to this category of **antipyretics** are described below.

A. Paracetamol INN, BAN, Acetaminophen USAN,

4′-Hydroxyacetanilide ; Acetamide, N-(4-hydroxyphenyl)- ; Paracetamol B.P., Eur. P., Acetaminophen U.S.P.,

Tylenol(R) (McNeil Consumer) ; Tapar(R) (Parke-Davis) ; SK-Apap(R) (Smith Kline & French) ; Valadol(R) (Squibb)

Synthesis



It may be prepared by the reduction of *p*-nitrophenol and the resulting *p*-aminophenol is acetylated by a mixture of acetic anhydride and glacial acetic acid. The crude product can be purified by recrystallization from a water : ethanol mixture (1 : 1) or from other appropriate solvents.

It is a metabolite of **acetanilide** and **phenacetin** employed as an anti pyretic and analgesic. It may be used effectively in a broad spectrum of arthritic and rheumatic conditions linked with musculoskeletal pain, headache, neuralgias, myalgias, and dysmenorrhea. It is particularly useful **in aspirin-sensitive patients.**

Dose : *Usual oral, adult, 500 mg to 1 g 3 or 4 times per day.*

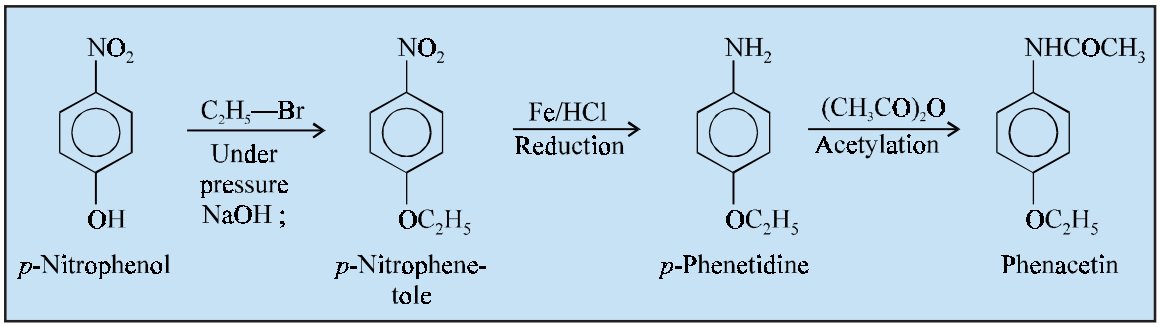
B. Phenacetin INN, BAN, USAN,

p-Acetophenetidide ; Acetamide, N-(4-ethoxyphenol)- ; Acetophenetidin ; *p*-Ethoxyacetanilid ; B.P. (1973), U.S.P., Eur. P., Int. P., Ind. P.

Synthesis

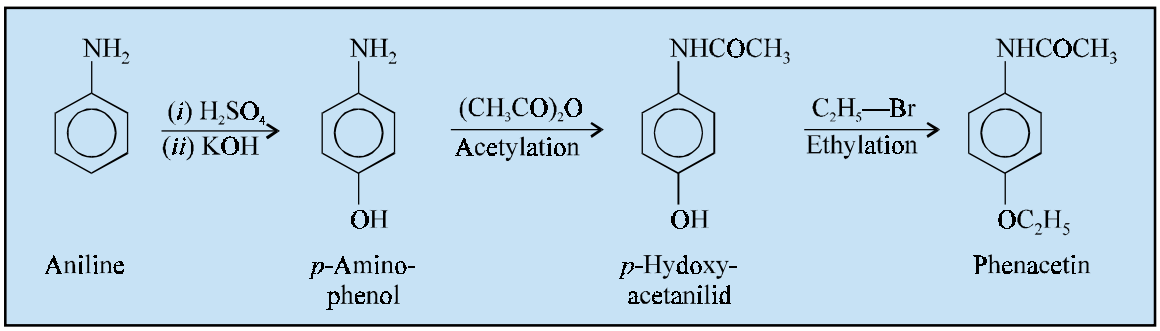
It may be prepared by any one of the following *three* methods, namely :

Method-I : From p-Nitrophenol



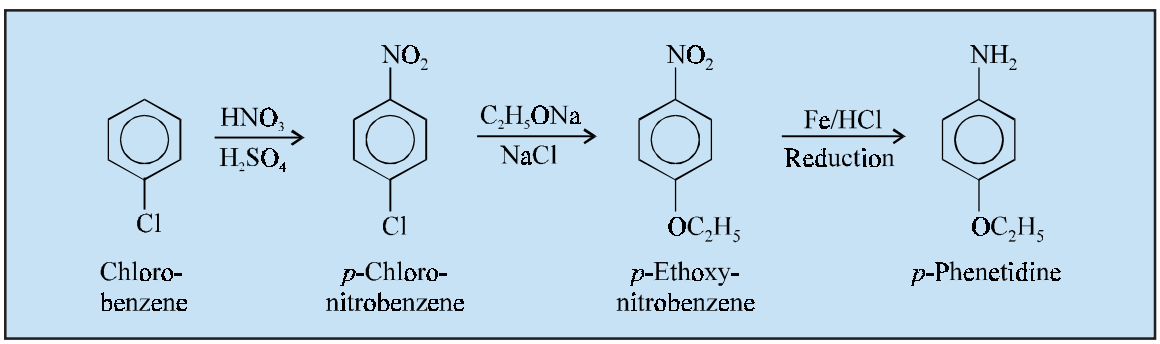
p-Nitrophenol, dissolved in sodium hydroxide solution, is subjected to condensation with ethyl bromide and the resulting *p*-nitrophenetole is reduced with suitable reductant. The *p*-phenetidine thus obtained is acetylated with acetic anhydride to yield the official compound.

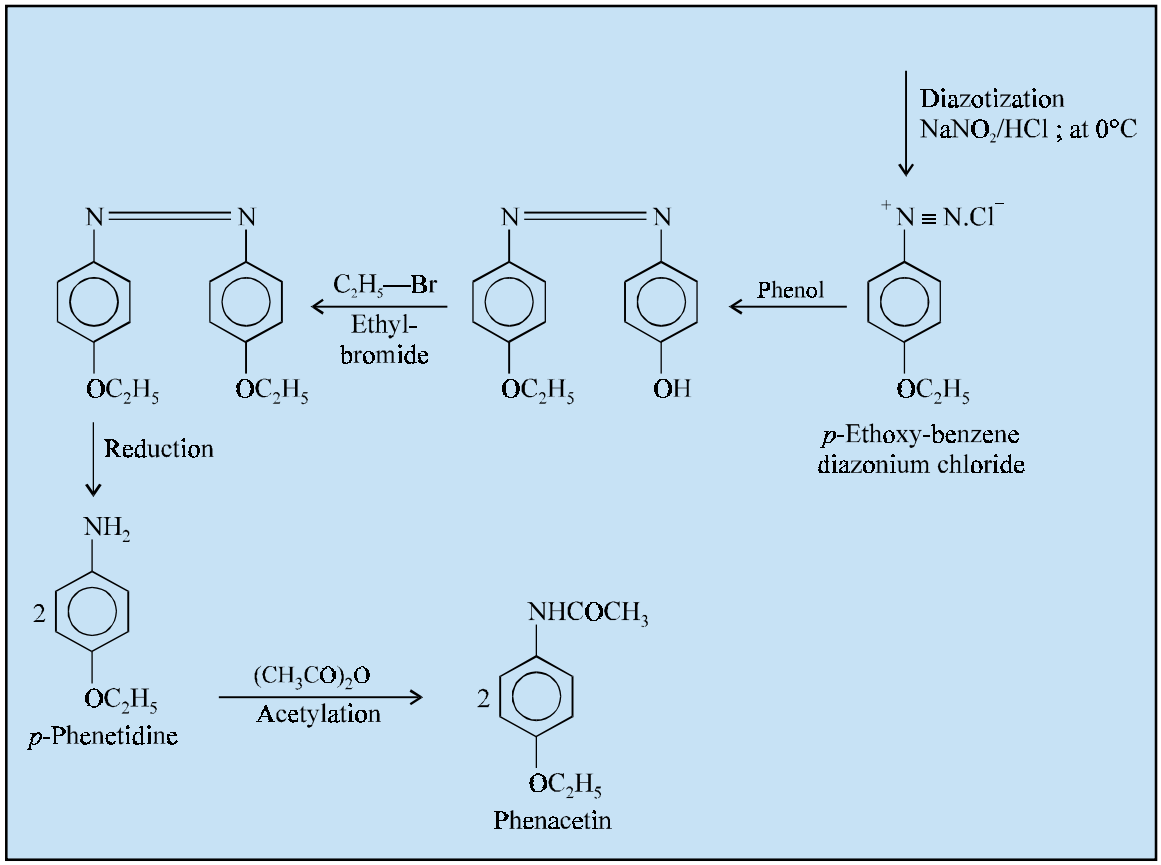
Method-II : From Aniline



p-Aminophenol is obtained by treating aniline with sulphuric acid and potassium hydroxide, which on acetylation with acetic anhydride yields the *p*-hydroxy acetanilide. The resulting product on ethylation with ethyl bromide forms **phenacetin.**

Method-III : From Chlorobenzene





p-Ethoxy nitrobenzene is prepared from chlorobenzene by its nitration followed by treatment with sodium ethoxide, which on reduction yields *p*-phenetidine. The resulting product is diazotised with nitrous acid at 0°C reacted with phenol, ethyl bromide and reduced to obtain two moles of *p*-phenetidine which upon acetylation with acetic anhydride yields two moles of **phenacetin**.

It is an analgesic and an antipyretic with similar effectiveness as **aspirin**. It has a greater potential for toxicity (hemolytic anemia and methemoglobinemia) than **paracetamol**. Irreversible kidney damage with prolonged ingestion of **phenacetin** has been established which ultimately resulted in complete withdrawal of this drug in many countries.

Dose : Usual, oral, adult, 300 mg to 2 g per day.

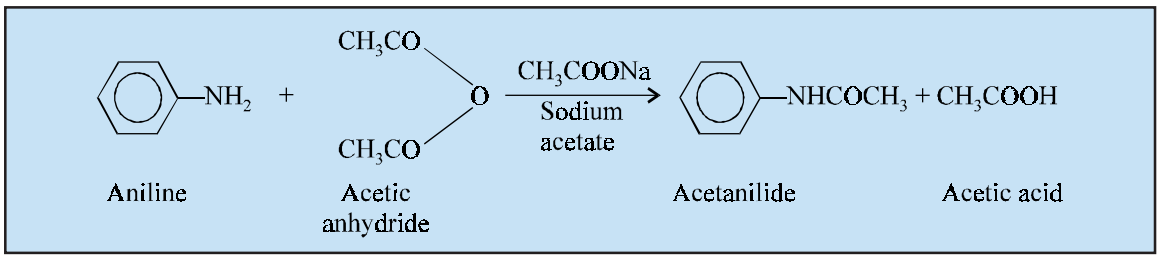
C. Acetanilide BAN, USAN,

N-Phenylacetamide ; Antifebrin ; B.P.C. 1949, N.F. X ;

Synthesis

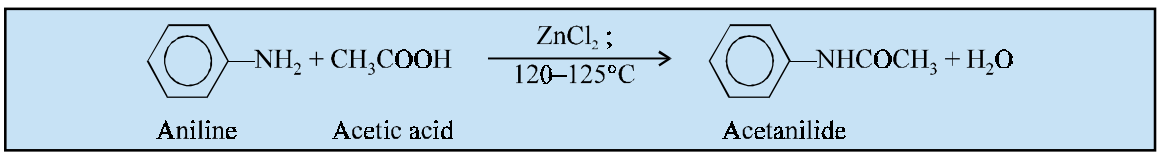
It may be prepared from aniline in two different ways, namely :

Method-I : From aniline and acetic anhydride



It may be prepared by the interaction of aniline and acetic anhydride in the presence of sodium acetate. The crude product may be recrystallized from alcohol.

Method-II : From aniline and acetic acid



It may also be prepared by reacting together redistilled aniline and glacial acetic acid in the presence of zinc chloride at an elevated temperature of 120-125°C.

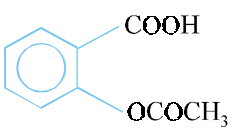
It is one of the cheapest antipyretic drugs. Owing to its high toxicity caused by liberation of free aniline *in vivo* it has been replaced by much safer antipyretics.

2.2. Salicylic Acid Analogues

Salicin was the first compound belonging to this category that exhibited medicinal value. It was employed as a substitute for quinine as a febrifuge. In 1838, Paria prepared salicyclic and whose structure was established by Hoffmann. Kolbe and Lautermann, (1860) introduced the commercial method of preparing salicyclic acid from sodium phenate. Acetylsalicylic acid or aspirin was first synthesized by Gerhardt in 1852, but unfortunately this wonder drug, more or less remained obscure until Felix Hoffmann studied its detailed pharmacodynamic properties in 1899. It gained entry into the world of medicine through Dreser, who coined a new name **'aspirin'** derived from "a" of acetyl and adding to it "spirin", an old name of **salicylic or spiric acid**, obtained from spirea plants.

A few classical of this series of compounds are discussed here.

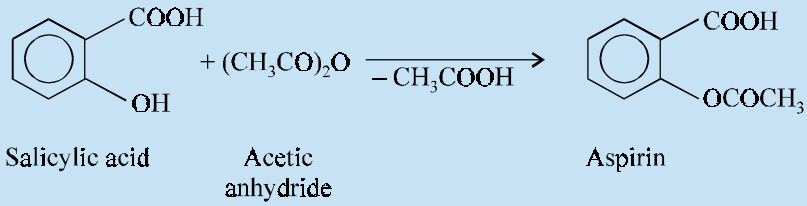
A. Aspirin BAN, USAN,



Salicylic acid acetate ; Benzoic acid, 2-(acetyloxy)- ; Acetylsalicylic acid ; *o*-Acetylsalicylic acid ; B.P., U.S.P., Eur. P., Int. P., Ind. P.,

Emipirin(R) (Burroughs Wellcome) ; A.S.A.(R) (Lilly) ; Bufferin(R) (Bristol-Myers)

Synthesis

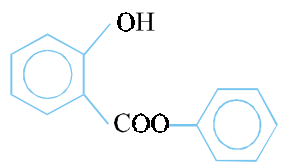


Acetylation of salicylic acid with acetic anhydride yields **aspirin**. The crude product may be recrystallized from benzene, mixture of acetic acid and water (1 : 1) or various other non-aqueous solvents.

It is used as an antipyretic anti-inflammatory and an analgesic in a variety of conditions ranging from headache, discomfort and fever associated with the common cold, and muscular pains and aches. **Aspirin** is regarded as the drug of choice in the reduction of fever because of its high degree of effectiveness and wide safety margin. As aspirin inhibits platelet function, it has been employed prophylactically to minimise the incidence of myocardial infarction and transient ischemic attacks.

Dose : *Usual, adult, oral 300 to 650 mg every 3 or 4 hours ; or 650 mg to 1.3 g as the sustained-release tablet every 8 hours ; Rectal, 200 mg to 1.3 g 3 or 4 times a day.*

B. Salol BAN, Phenyl Salicylate USAN.



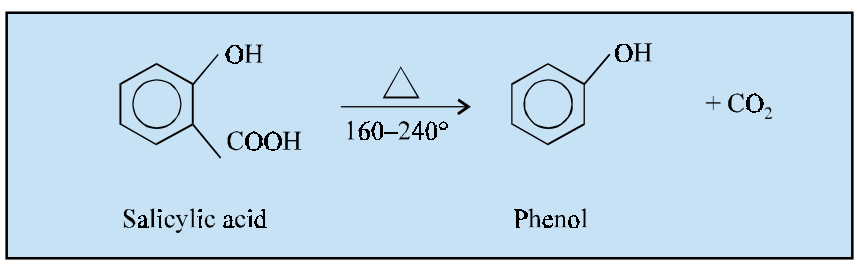
Sola-Stick$^{(R)}$ (Hamilton) ;

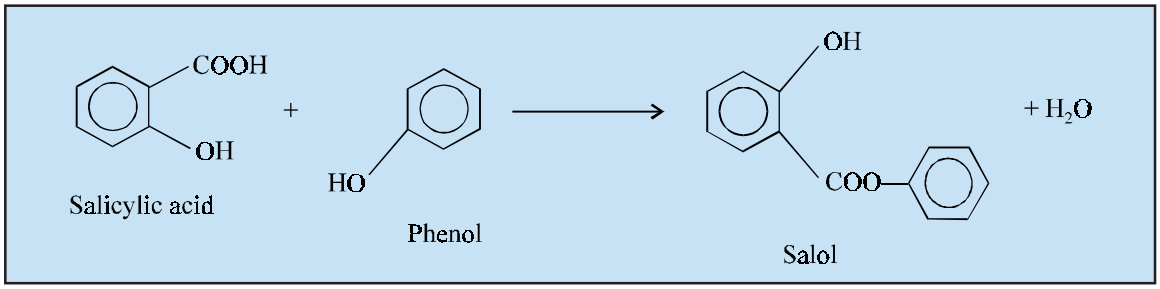
B.P.C. 1954, N.F. XI

Synthesis

It may be prepared by either of the *two* following methods :

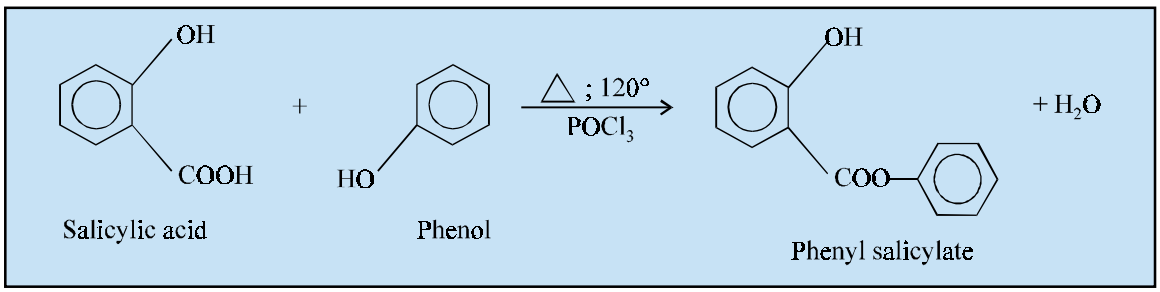
Method-I : By heating salicylic acid alone





It may be prepared by heating salicylic acid at 160–240°C under vacuum and distilling off the water formed as a by-product.

Method-II : By heating salicylic acid and phenol



It may be prepared by heating together salicylic acid and phenol at 120°C in the presence of phosphorus oxychloride or carbonyl chloride ($COCl_2$).

Salol was first introduced as a drug in 1886 by Nencki. It may be employed as an antipyretic and also as internal antiseptic, but effective doses were toxic owing to the liberation of phenol. It is not usually hydrolysed in the stomach but in the intestine it gradually gets hydrolysed into salicylic acid and phenol respectively. The liberated phenol exerts antiseptic action without any undue toxic effect. Thus the administration of drugs on the above criterion is commonly termed as **'salol principle'** or **'Nencki principle'.** Drugs used on salol principle are generally classified under *two* categories, namely : **true salols and partial salols.**

True Salols—are such compounds in which both the compounds *e.g.*, acid and phenol or alcohol are pharmacologically active. **Examples : Salol** and ; **betol (β-naphthyl salicylate).**

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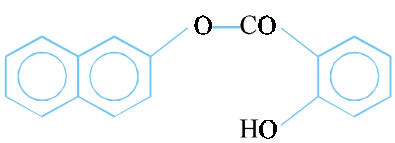
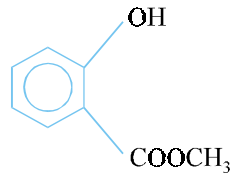


Betol

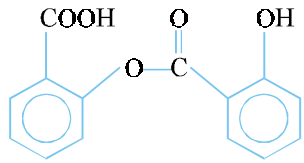
Partial Salols—are such compounds wherein either the acid or the hydroxylic moiety is active pharmacologically.

Example : Methyl salicylate (oil of wintergreen) in which the salicylic acid constitutes the active component.



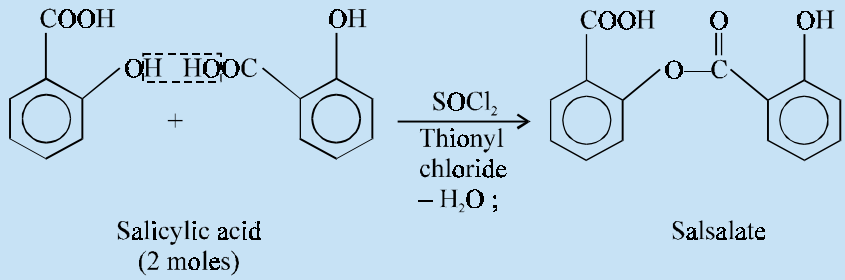
Methyl salicylate

C. Salsalate INN, BAN, USAN.



Salicylic acid, biomolecular ester ; Benzoic acid, 2-hydroxy-, 2-carboxyphenyl ester ; *o*-(2-Hydroxybenzoyl) salicylic acid ; Salicylosalicylic acid ; Sasapyrine ; Salicyl Salicylate ; Salysal ; Disalacid(R) (Riker) ; Saloxium(R) (Whitehall)

Synthesis

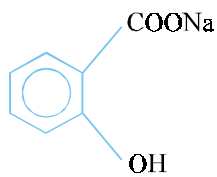


It is prepared by the condensation of two moles of salicylic acid in the presence of thionyl chloride.

It has antipyretic, analgesic and anti-inflammatory properties similar to those of aspirin. It is employed in the **treatment of rheumatoid arthritis and other rheumatic disorders.**

Dose : *Usual, adult, oral 325 to 1000 mg 2 to 3 times per day.*

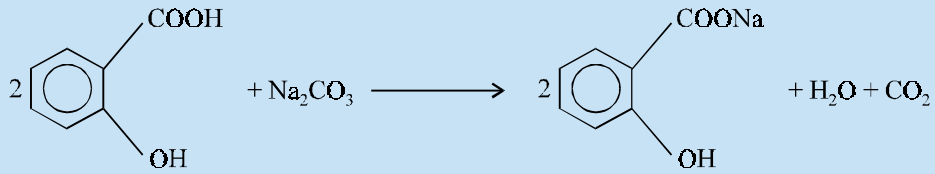
D. Sodium Salicylate BAN, USAN.



Monosodium salicylate ; Benzoic acid, 2-hydroxy-, monosodium salt ; B.P., U.S.P., Eur. P., Int. P., Ind. P.,

Entrosalyl (Standard)(R) (Cox Continental, U.K.)

Synthesis



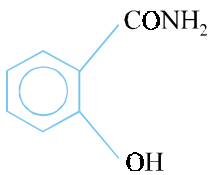
Salicylic acid — Sodium salicylate

It may be prepared by mixing together a paste of salicylic acid in distilled water with sufficient pure sodium carbonate in small lots at intervals. The reaction mixture is filtered through iron-free filter paper and evaporated to dryness under reduced pressure. Caution must be taken to avoid contact with iron which will alter the original white colour of the product.

It is generally used for the reduction of fever and the relief of pain. It also possesses anti-inflammatory actions similar to aspirin. It is recommended in acute rheumatic fever and in the symptomatic therapy of gout.

Dose : *In rheumatic fever, 5 to 10 g daily in divided doses.*

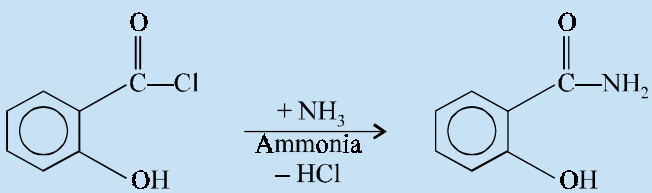
E. Salicylamide INN, BAN, USAN,



o-Hydroxybenzamide ; N.F. XIII ;

Salined(R) (Medo-Chemicals, U.K.)

Synthesis



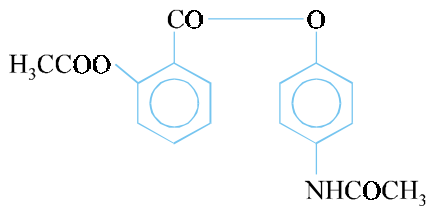
Salicyl chloride — Salicylamide

It is readily prepared from the interaction of salicyl chloride and ammonia.

Its antipyretic and analgesic activity is not more than that of **aspirin**. It may be used in place of salicylates where apparent sensitivity occurs with the latter.

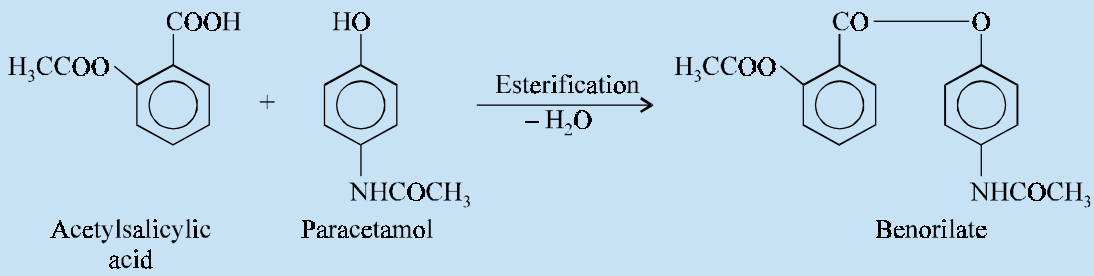
Dose : *300 mg to 1 g, 3 times per day.*

F. Benorilate INN, BAN, USAN, Benorylate BAN,



4-Acetamidophenyl salicylate acetate ; 4-Acetamidophenyl-*o*-acetyl-salicylate ;
Fenasprate ; Benoral(R) (Winthrop)

Synthesis

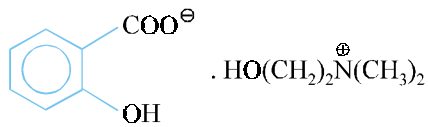


It may be prepared by the esterification of **acetyl salicylic acid** and **paracetamol** with the elimination of a mole of water.

It possesses antipyretic, analgesic and anti-inflammatory properties. It is employed in the treatment of rheumatic disorders and in moderate pain, and as an antipyretic.

Dose : *Rheumatic conditions 1.5 g, 3 times daily.*

G. Choline Salicylate, INN, BAN, USAN,

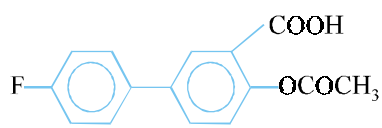


(2-Hydroxymethyl) trimethyl ammonium salicylate ;
Arthropan(R) (Purdue Frederick)

It possesses actions similar to those of **aspirin** but it is mainly used as a local analgesic by being applied to the painful area by gentle rubbing.

Dose : *Adult, usual 0.87 to 1.74 g, 3 or 4 times daily.*

H. Flufenisal INN, USAN,



Acetyl-5-(4-fluorophenyl) salicylic acid ; 4′-Fluoro-4-hydroxy-3-biphenyl-carboxylic acid acetate ; [1, 1′-Biphenyl]-3-carboxylic acid, 4-(acetyloxy)-4′-fluoro- ;

Flufenisal$^{(R)}$ (MSD).

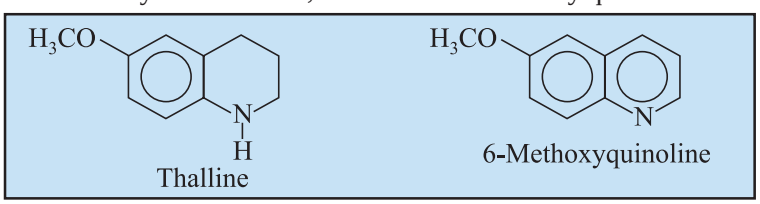
The search for a better drug than aspirin with increased potency, longer duration of action and having less effect on gastric secretion gave birth to flufenisal which essentially has a hydrophobic moiety at C_5. In man, it exhibits a two-fold increase in potency and duration of action than that of aspirin.

Dose : *150 to 300 mg every 3 or 4 hours.*

2.3. Quinoline Derivatives

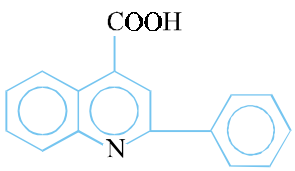
The historical importance and utility of quinine was known in the medical practice for a long time as a potent antipyretic in addition to its remarkable effect against the malarial fever. The basic quinoline nucleus, present in the **quinine** molecule, contributes to antipyretic activity to a certain extent. Therefore, an attempt was made to synthesize a number of quinoline derivatives which might exhibit better antipyretic activity.

Two quinoline derivatives first synthesized though possessed significant antipyretic action, yet could not gain cognizance as a drug because of their high toxic effects on the red blood corpuscles and damaging after-effect on kidneys. These were, thalline and 6-methoxy quinoline.



Thalline 6-Methoxyquinoline

A. Cinchophen INN, BAN, USAN,

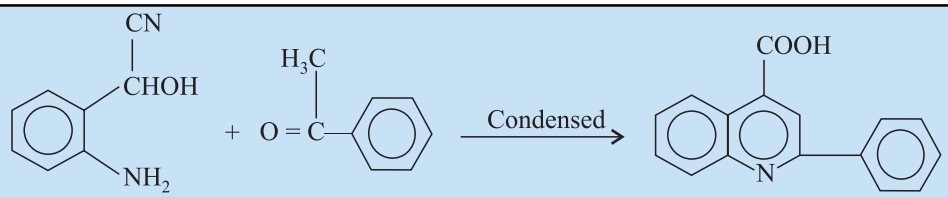


2-Phenyl-cinchoninic acid ; 2-Phenylquinoline-4-carboxylic acid ; Quinophan ; Atophan ; B.P. 1953, N.F. X.

Synthesis

It may be prepared by any one of the following *three* methods :

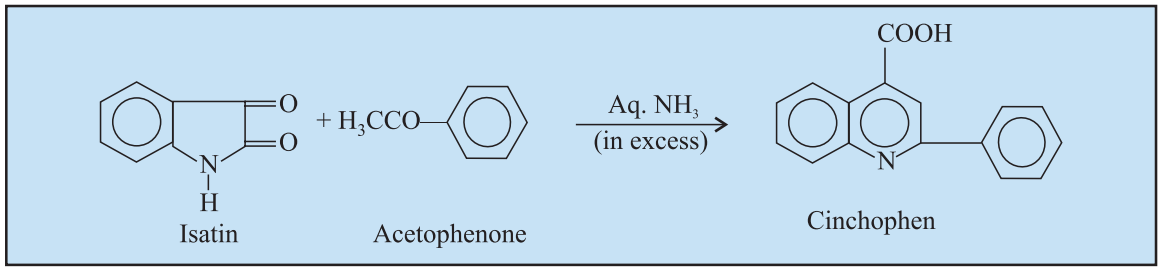
Method-I : From o-Amino benzaldehyde cyanohydrin



o-Aminobenzaldehyde cyanohydrin Methyl-phenyl ketone Cinchophen

Condensation of *o*-aminobenzaldehyde cyanohydrin and methylphenyl ketone yields **cinchophen.**

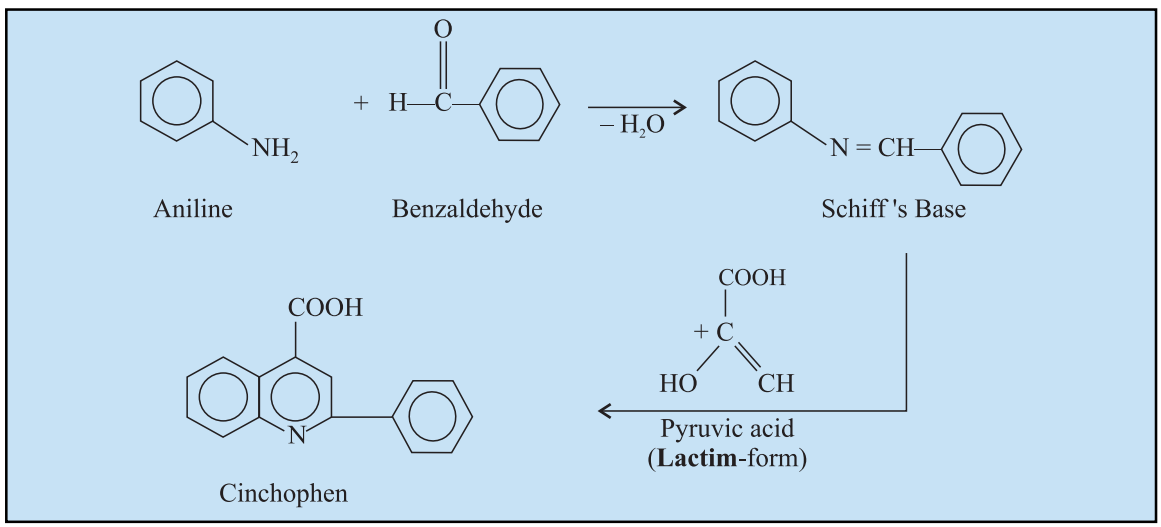
Method-II : From Isatin



Cinchophen may be prepared by the interaction of isatin and acetophenone in the presence of excess of aqueous ammonia.

Method-III : From Aniline

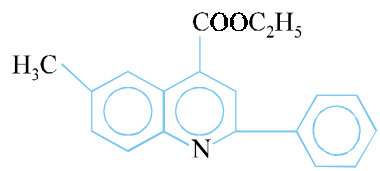
The **Schiff's base** is prepared by the interaction of aniline and benzaldehyde with the elimination of a molecule of water. The resulting base is treated with the *lactim*-form of pyruvic acid thereby resulting into the formation of **cinchophen.**



Cinchophen possesses antipyretic actions similar to those of the salicylates. It was chiefly used **in the treatment of chronic gout and rheumatic conditions but because of its high toxicity, e.g., liver damage resulting in acute jaundice, it has been completely withdrawn and replaced by safer drugs.**

Dose : *300 to 600 mg.*

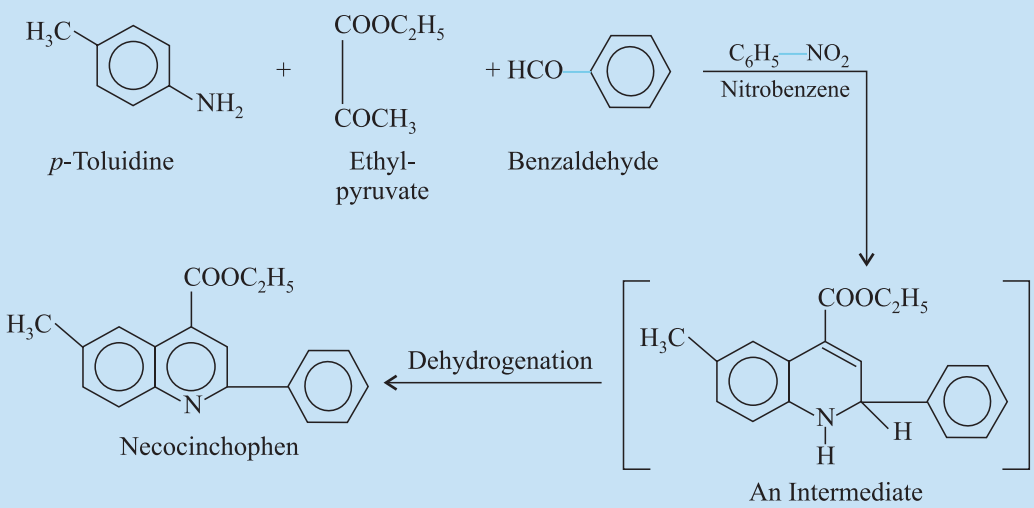
B. Neocinchophen INN, BAN, USAN



Ethyl-6-methyl-2-phenyl-4-quinolinecarboxylate ; N.F. XI ;

Tolysin(R) (Lederle)

Synthesis



It occurs through the reaction of *p*-toluidine, ethyl pyruvate and benzaldehyde in the presence of a small amount of nitrobenzene, when the products get condensed to form an intermediate compound. This when subjected to dehydrogenation yields **neocinchophen.**

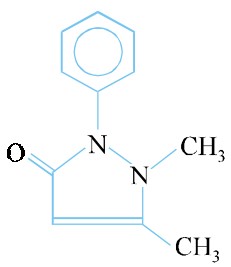
It has been used for the same purposes as **cinchophen**.

Dose : *500 mg.*

2.4. Pyrazolones and Pyrazolodiones

One of the first and foremost synthetic organic compounds which were successfully used as drugs was found to be a heterocycle. It is, however, worthwhile to mention here that the pharmacodynamic spectrum of both the above categories of heterocyclic compounds has a close resemblance to that of aspirin. A few such compounds belonging to either of the said classes are discussed here.

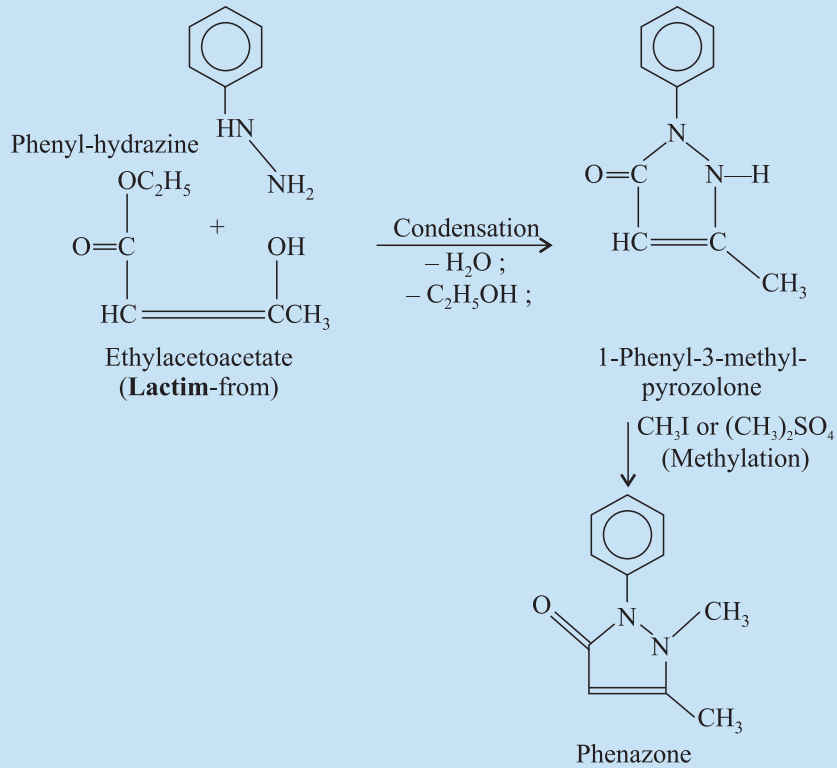
A. Phenazone INN, BAN, Antipyrine USAN,



2, 3-Dimethyl-1-phenyl-3-pyrazolin-5-one ; 1, 2-Dihydro-1, 5-dimethyl-2-phenyl-3H-pyrazol-3-one ; Antipyrin ; Phenazone B.P., Eur. P., Int. P., Antipyrine U.S.P.

Component of Auralgan(R) (Ayerst) ; Areumal(R) (as Gentisate ; Ecobi. Italy)

Synthesis

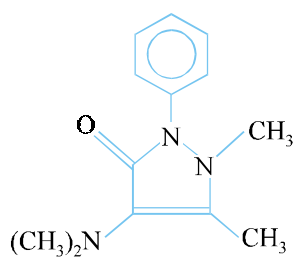


It may be prepared by the condensation of one mole each of phenyl-hydrazine and the *lactim*-form of ethylacetoacetate when 1-phenyl-3-methyl-pyrazolone is obtained by the elimination of a mole each of water and ethanol. The resulting product is subjected to methylation either with methyl iodide or dimethyl sulphate to yield **phenazone.**

As antipyretic, it possesses local anaesthetic and styptic actions and solutions containing 5% are used locally as ear drops. It has now been replaced by relatively more effective and safer drugs.

Dose : 300 to 600 mg.

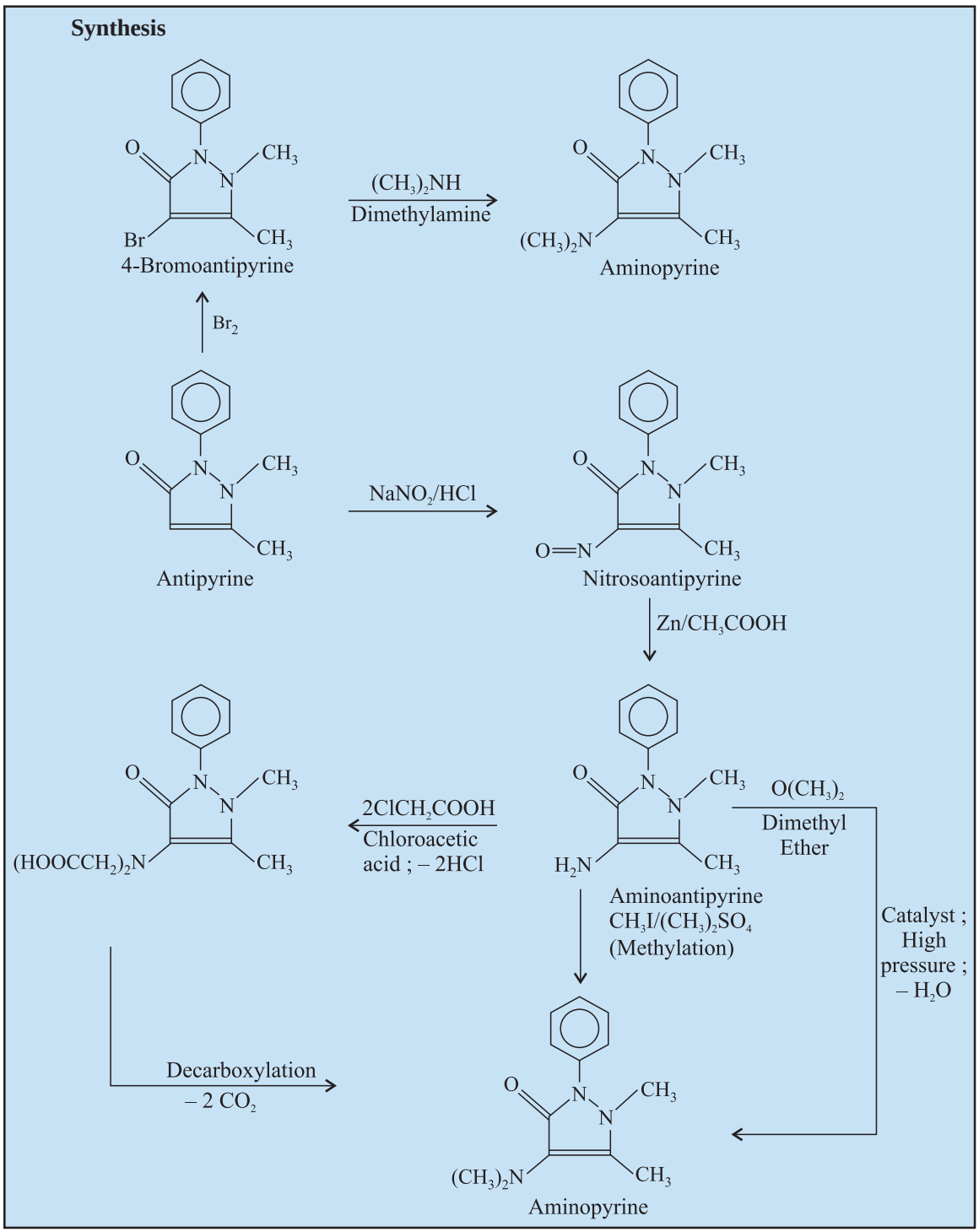
B. Aminophenazone INN, Amidopyrine BAN, Aminopyrine USAN,



4-Dimethylamino-2, 3-dimethyl-1-phenyl-3-pyrazolin-5-one ; 4-Dimethyl-amino-1, 5-dimethyl-2-phenyl-4-pyrazolin-3-one ; Dimethylaminoantipyrine ; Dimethylaminophenazone ; Amidopyrine B.P.C. 1954, Eur. P., Int. P., Aminopyrine N.F.X. ;

Piramidon$^{(R)}$ (Hoechst, Spain)

Synthesis



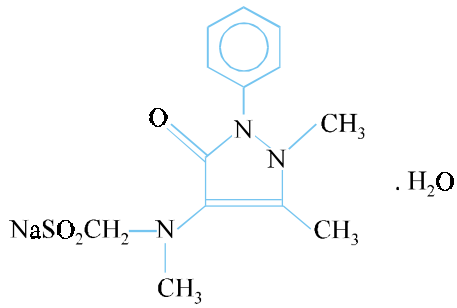
Aminopyrine (amidopyrine) may be prepared commercially first by treating **antipyrine** with nitrous acid to yield nitrosoantipyrine. The resulting product can now be routed through two different course of reactions, namely : (*a*) treatment with two moles of chloroacetic acid followed by decarboxylation

producing thereby aminopyrine ; and (*b*) treatment with dimethyl ether in the presence of catalyst and at high pressure eliminates a mole of water to give aminopyrine. However, aminopyrine can be prepared conveniently in the laboratory by first treating antipyrine with bromine partially to obtain 4-bromo-antipyrine which on subsequent treatment with dimethylamine yields the official compound.

It has antipyretic actions similar to those of phenazone but owing to the risk of agranulocytosis its use is discouraged and mostly abandoned. However, the gentisate has sometimes been used. **Aminopyrine** is often employed in drug metabolism studies.

Dose : *300 to 500 mg ; max in 24 hours 3 g.*

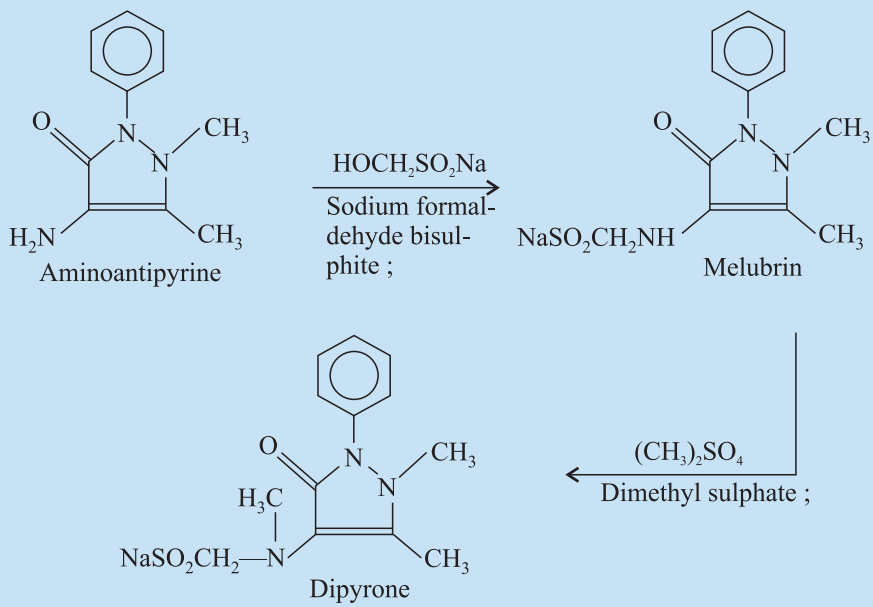
C. Dipyrone BAN, USAN, Noramidopyrine Methanesulfonate Sodium INN,



Sodium (antipyrinylmethylamino) methanesulfonate monohydrate ; Methane-sulfonic acid, [(2, 3-dihydro-1, 5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl) methylamino]-, sodium salt, monohydrate ; Analginum ; Metamizol ; Amino-pyrine-sulphonate sodium ;

Novalgin(R) (Hoechst) ; Novaldin(R) (Winthrop)

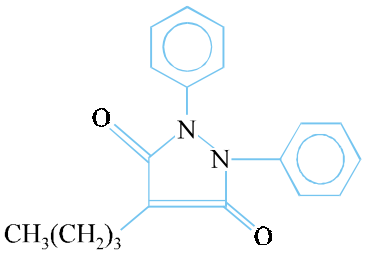
Synthesis



It possesses similar properties to that of amidopyrine. Its use is really justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable. Its use is restricted in some countries.

Dose : *Usual, 0.5 to 1 g, 3 times per day.*

D. Phenylbutazone INN, BAN, USAN,

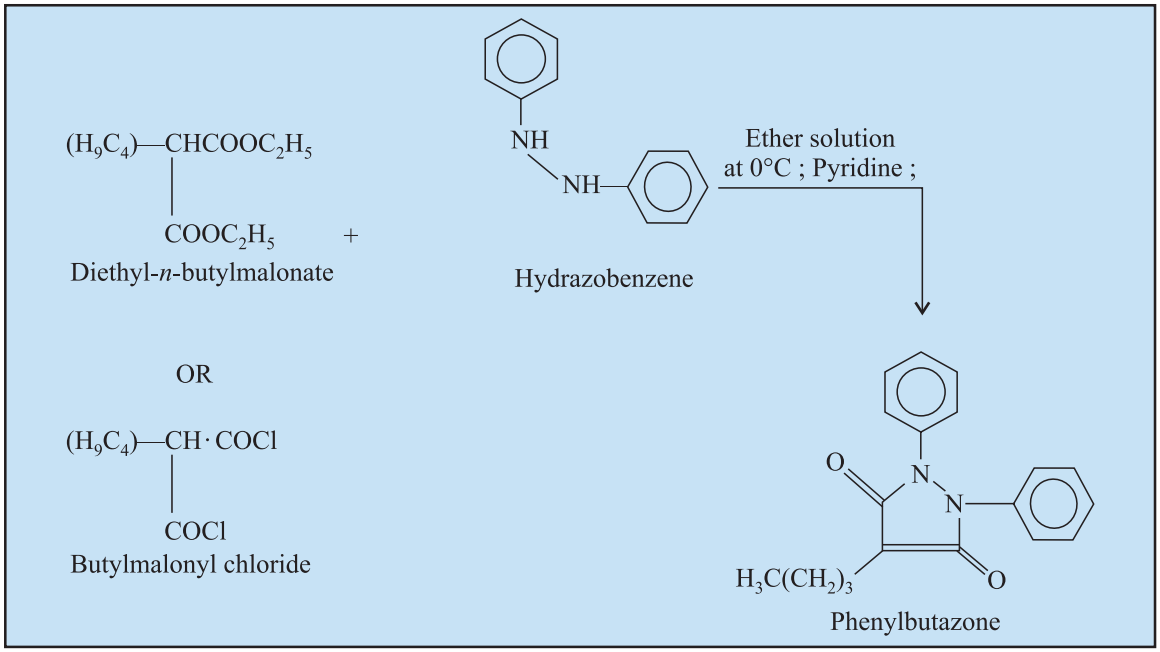


4-Butyl-1, 2-diphenyl-3, 5-pyrazolidinedione ; 3, 5-Pyrazolidinedinedione, 4-butyl-1, 2-diphenyl- ; Butadione ; B.P., U.S.P., Eur. P., Int. P.,

Butazolidin(R) (Ciba-Geigy) ; Busone(R) (Reid-Provident)

Synthesis

Phenylbutazone may be prepared by condensation either from diethyl-*n*-butyl malonate or *n*-butyl malonyl chloride with hydrazobenzene in either solution at 0°C with the aid of pyridine. Subsequently, the pyridine is extracted with aqueous hydrochloric acid, the phenylbutazone is extracted with aqueous sodium bicarbonate and finally precipitated by addition of hydrochloric acid.

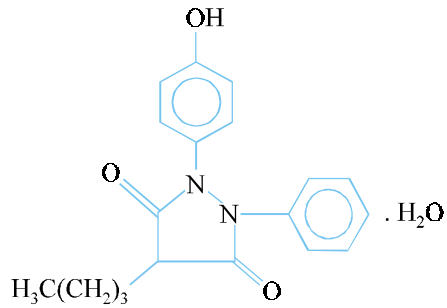


It is a pyrazole derivative which has antipyretic, analgesic and anti-inflammatory actions, because of its toxicity it is not used as a general antipyretic or analgesic. It is, an usual practice, reserved for use in the treatment rheumatic disorders, such as : osteoarthrosis, rheumatoid arthritis, ankylosing spondylitis, arthritis, acute superficial thrombophlebitis, painful shoulder and Reiter's disease, where less toxic drugs have failed.

In some countries, its use and that of oxyphenbutazone are now restricted to only ankylosing spondylitis.

Dose : *100 to 600 mg per day.*

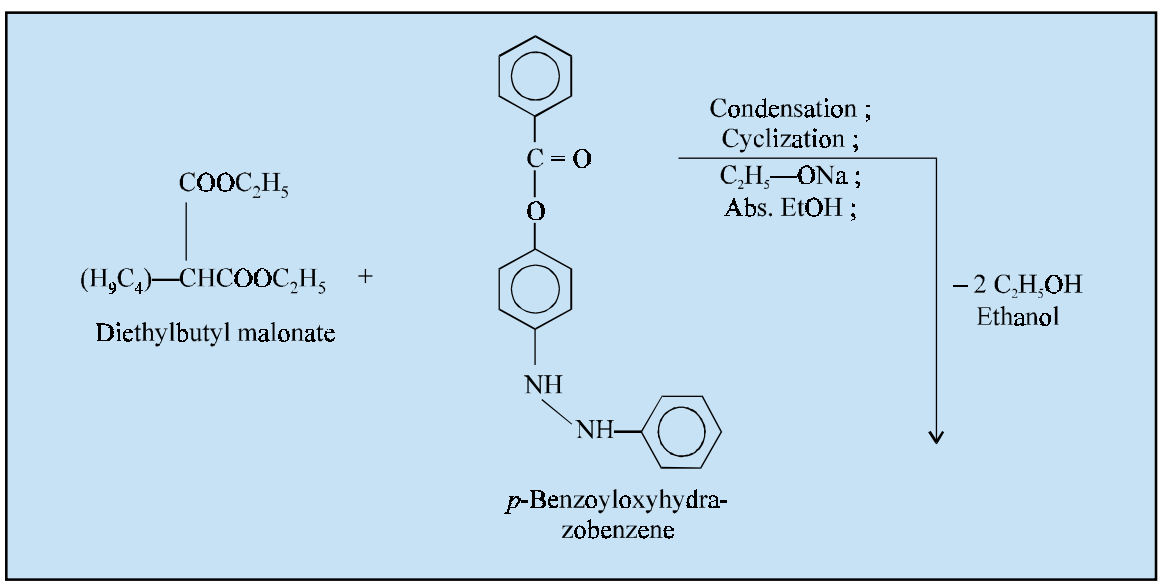
E. Oxyphenbutazone INN, BAN, USAN,



4-Butyl-1-(*p*-hydroxyphenyl)-2-phenyl-3, 5-pyrazolidinedione monohydrate ; 3, 5-Pyrazolidinedione, 4-butyl-1-(4-hydroxyphenyl)-2-phenyl, monohydrate ; B.P., U.S.P., Tandearil$^{(R)}$ (Ciba-Geigy) ; Oxalid$^{(R)}$ (USV).

Synthesis

Condensation of diethyl butyl malonate and *p*-benzyloxyhydrazo-benzene is done in the presence of sodium ethoxide in anhydrous ethanol to yield 1-(benzyloxy)-2-phenyl-4-butyl-3, 5-pyrazolidinedione. The reaction mixture is heated with xylene to about 140°C for several hours which aids in the removal ethanol eliminated by cyclization. The resulting product is debenzylated by the aid of Raney Nickel hydrogenation at an ambient temperature and pressure. The crude product may be recrystallized from ether/petroleum ether.



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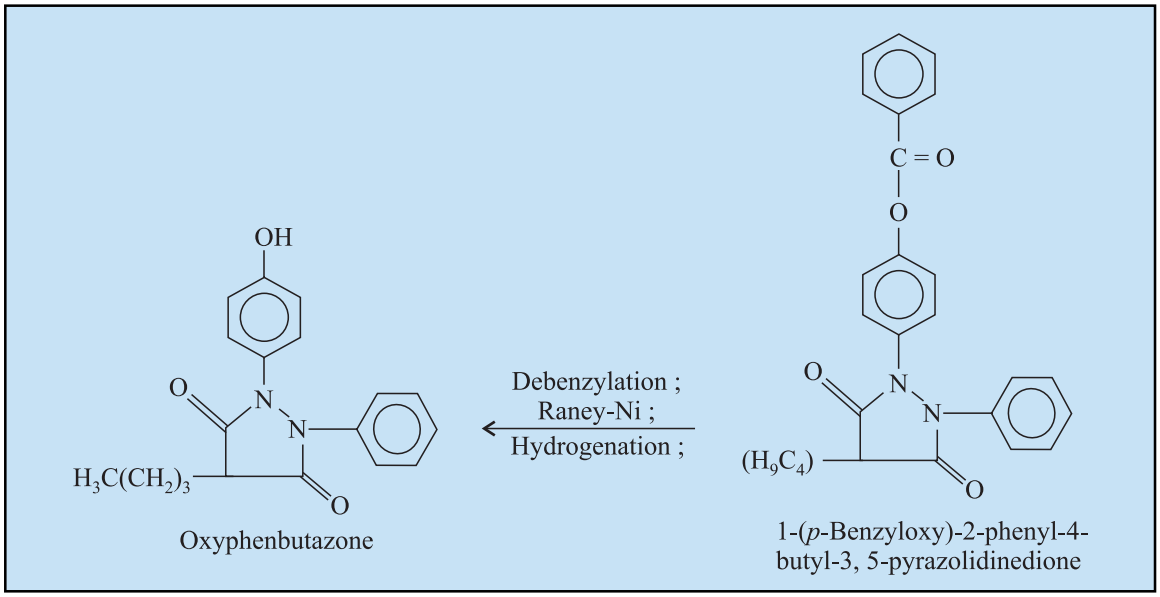
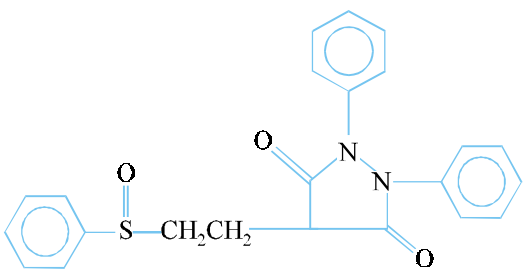


It is a metabolite of **phenylbutazone** and possesses the same antipyretic, analgesic, anti-inflammatory and mild uricosuric actions as the parent compound. It also finds its use in rheumatic and other musculo-skeletal disorders. It has also been recommended in the management of thrombophlebits.

Dose : *Usual, oral, adult, antirheumatic, 100 or 200 mg 3 times daily ; maintenance 100 mg 1 to 4 times daily ; antigout, 400 mg initially as a loading dose, then 100 mg every 4 hours.*

F. Sulfinpyrazone INN, USAN, Sulphinpyrazone BAN.



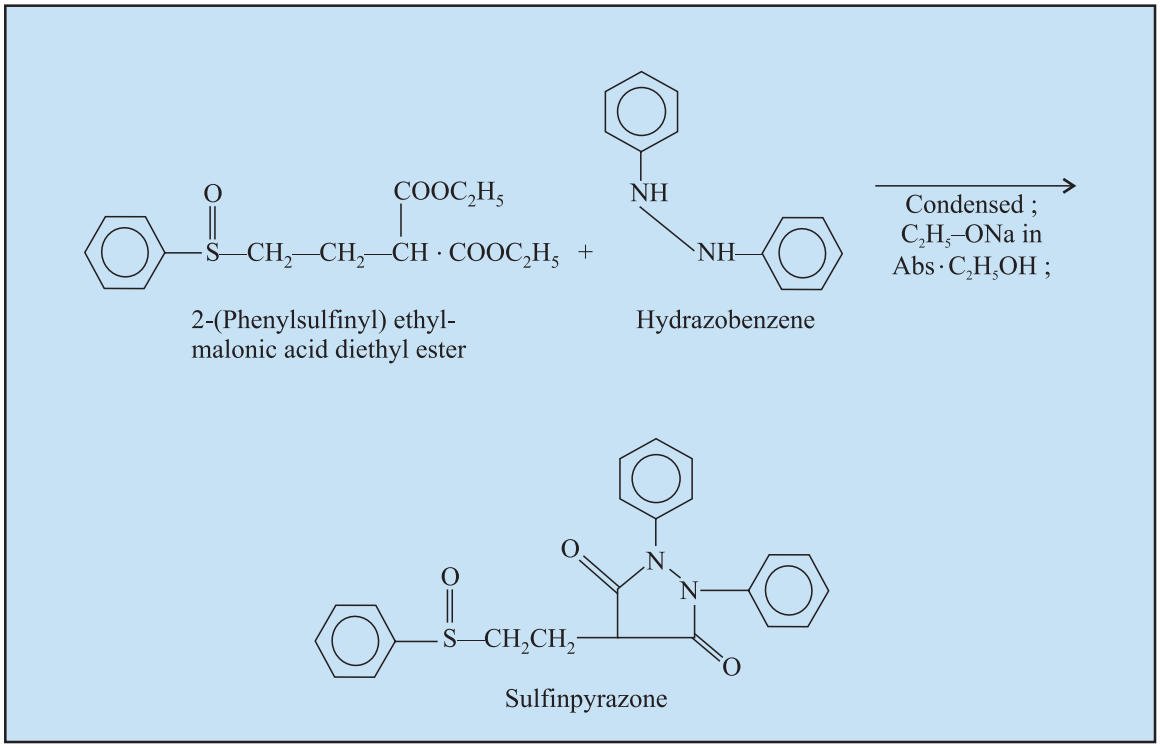
1, 2-Diphenyl-4[2-(phenylsulfinyl) ethyl]-3, 5-pyrazolidinedione ; 3, 5-Pyrazolidinedione, 1, 2-diphenyl-4-[2-(phenylsulfinyl) ethyl]- ; B.P.,

U.S.P., Anuturane$^{(R)}$ (Ciba-Geigy)

Synthesis

It may be prepared by the condensation of [2-(phenylsulfinyl) ethyl]- malonic acid diethyl ester with hydrazobenzene in the presence of sodium ethoxide in absolute ethanol. Completion of reaction is achieved by the addition of xylene and subsequent heating at about 130°C whereby the ethanol liberated as a product of condensation is removed completely. The crude product is extracted with a suitable solvent and finally recrystallized from ethanol.

It is a **uricosuric agent** structurally related to phenylbutazone. It is normally employed for the long term **treatment of chronic gout where it effects slow depletion of urate tophi in the tissues.**

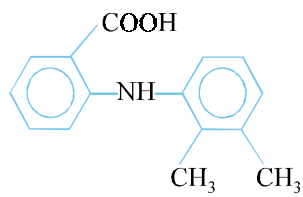


Dose : *Initial oral dose 100 to 200 mg per day, taken with meals or milk.*

2.5. The N-Arylanthranilic Acids

The structural analogues of **N-arylanthranilic** acid opened an altogether new horizon of antipyretic, analgesic and anti-inflammatory compounds which have recently gained recognition in the therapeutic armamentarium. A few compounds belonging to this category are discussed here.

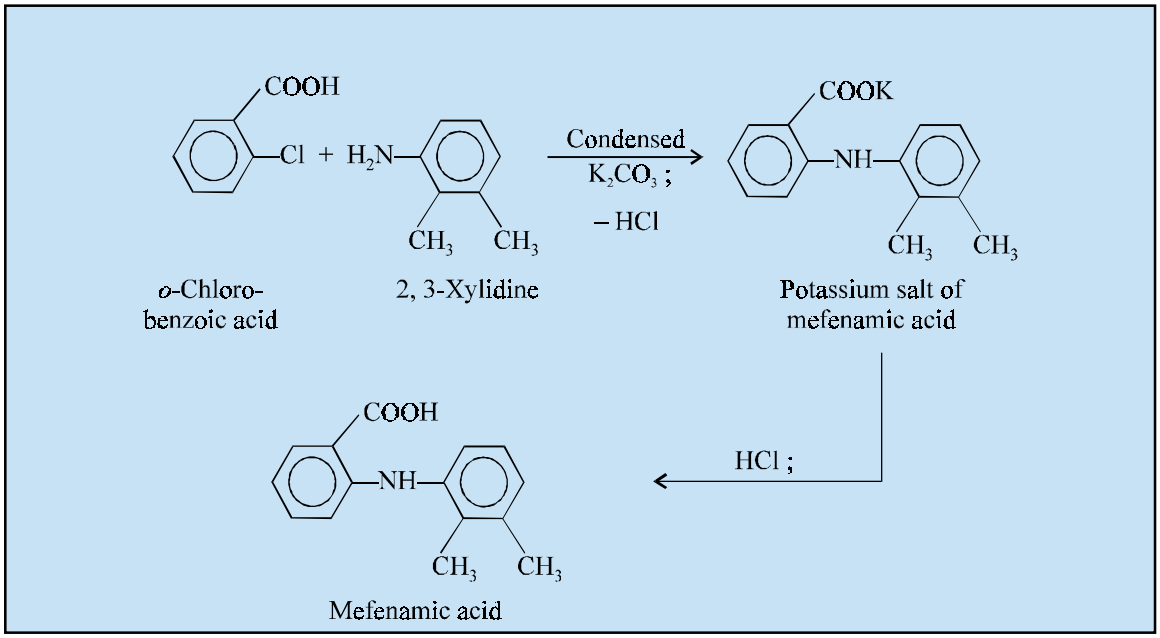
A. Mefenamic Acid BAN,



N-(2, 3-Xylyl) anthranilic acid ; Benzoic acid, 2-[(2, 3-dimethylphenyl) amino]- ; B.P., Ponstel$^{(R)}$ (Parke-Davis).

Synthesis

It may be prepared by the condensation of *o*-chlorobenzoic acid with 2, 3-xylidine in the presence of potassium carbonate to give the potassium salt of mefenamic acid, which on treatment with hydrochloric acid yields the official compound.

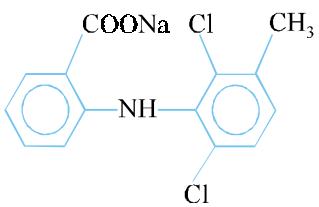


It is an analgesic drug usually indicated for the treatment of primary dysmenorrhea, mild pain and for pain due to dental extractions.

Dose : *Usual, adults, children over 14 years of age, oral, 500 mg, followed by 250 mg 4 times daily.*

(Caution : Must not be used for more than 7 days).

B. Meclofenamate Sodium BAN, USAN, Meclofenamic Acid INN.



Monosodium N-(2, 6-dichloro-*m*-tolyl) anthranilate monohydrate ; Benzoic acid, 2-[2, 6-(dichloro-3-methylphenyl) amino]-, monosodium salt ; U.S.P.,

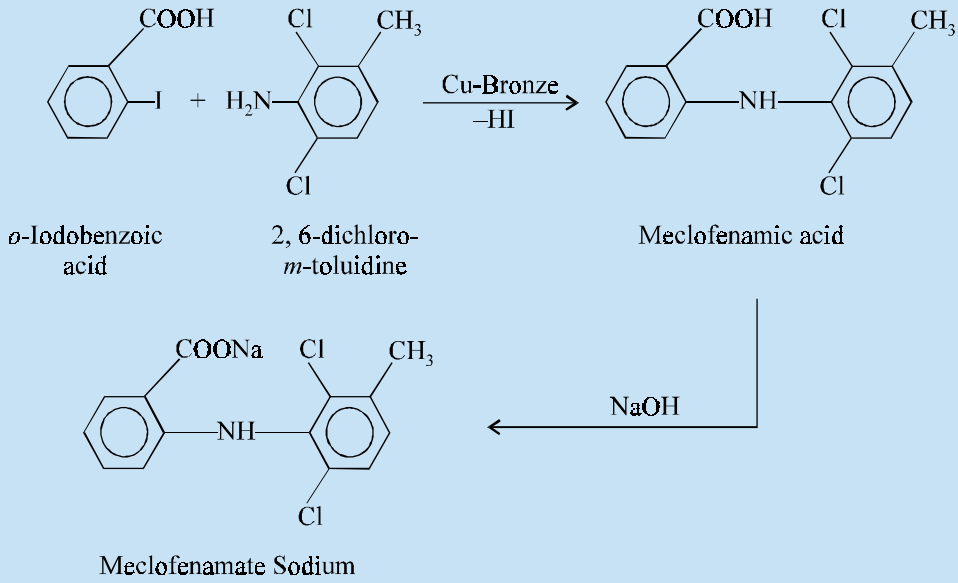
Meclomen$^{(R)}$ (Parke-Davis).

Synthesis :

It may be prepared by the **Ulman Condensation** of *o*-iodobenzoic acid with 2, 6-dichloro-*m*-toluidine in the presence of copper-bronze resulting into the formation of meclofenamic acid which on neutralization with equimolar proportion of sodium hydroxide yields **meclofenamate sodium.**

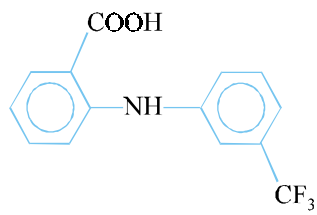
It possesses analgesic, anti-inflammatory, and antipyretic properties. It is used for the **treatment of acute and chronic rheumatoid arthritis and osteoarthritis.**

Synthesis



Dose : *Usual, oral, 200 to 400 mg daily in 3 or 4 equal doses.*

C. Flufenamic Acid INN, BAN, USAN.



N-(α, α, α-Trifluoro-*m*-tolyl)-anthranilic acid ; Benzoic acid, 2-[[3-(trifluoro-methyl) phenyl] amino]- ; B.P., U.S.P.,

Meralen(R) (Merrell, U.K.)

It has analgesic, anti-inflammatory and antipyretic actions. It is employed in the **treatment of rheumatic disorders** and dysmenorrhoea.

Dose : *400 to 600 mg per day in divided doses.*

3. MECHANISM OF ACTION

The **'drugs'** included in this chapter essentially possess solely the **'antipyretic and analgesic'** pharmacological actions but specifically lack anti-inflammatory effects.

Interestingly, the **'antipyretic'** activity is exclusively caused due to the direct interferences, with such phenomena with the aid of which **'pyrogenic factors'** give rise to **fever** ; however, they are found

absolutely unable to bring-down the elevated body temperature (>> 98.4°F) specifically in a febrile subjects. It has already been established beyond any reasonable doubt that the **'antipyretics',** in general, exert their activities very much within the CNS. These pharmacological actions are significantly located at the **'hypothalamic thermoregulatory centre'** ; however, recent studies categorically advocates the **'peripheral actions'** may also contribute enormously and positively.

In fact, there are *two* different school of thoughts that have been suggested to explain the modalities of antipyretic action :

(*a*) **Endogenous leukocytic pyrogens** are presumably released from the cells that have been duly activated by a host of stimuli, and '*antipyretics*' do exert their action by inhibiting the corresponding activation of these cells by an exogenous pyrogen, and

(*b*) Inhibition of the release of **'endogenous leukocytic pyrogens'** from the cells as soon as these have been adequately activated by the exogenous pyrogen.

Clark* (1979) put forward substantial evidences to prove that there exists a **'central antipyretic mechanism'** which specifically affords an **'antagonism'** that may be caused on account of :

(*i*) A direct competition ensuing of a pyrogen and the antipyretic drug pervailing at the CNS-receptors, and

(*ii*) An inhibition of prostaglandin (PG) synthesis occurring in the CNS.

More logistically, the experimental pharmacologists usually determine the *analgesic activity* in laboratory animals (rat/mice) by measuring the **'pain threshold'** in terms of certain reflex actions essentially produced by noxious stimuli, for instance : pressure, heat and electric shock. There are several, known methods to determine the exact **'analgesic profile'** in **'synthetic'** as well as **'natural plant products',** such as : rat tail-flick test ; mouse hot-plate test ; and usage of electricity to tooth-pulp thereby giving rise to almost reproducible results (*i.e.*, end-points) whose appearance may be delayed with respect to '*time*' by **'analgesic drugs'** under examination virtually with a direct relationship to both the **potency** and **efficacy**.

Hughes and Kosterlitz** (1975) isolated (from pig-brain) and identified **'enkephalins'** produced in the body having narcotic-like substances so as to react judiciously with receptors for the narcotic drugs. Thus, the two identified and characterized **'brain-peptides'** essentially differed only in the nature of their N-terminal amino acids, for instance : (*a*) **methionin-enkephalin**-having a tyrosine-glycine-glycine-phenylalamine-methionine sequence ; and (*b*) **leucine-enkephalin**-having a tyrosine-glycine-glycine-phenylalanine-leucine sequence.

4. MECHANISM OF ACTION OF SELECTED ANTIPYRETIC-ANALGESICS

The mechanism of action of certain selected **antipyretic-analgesics** included in this chapter (section 10.2) are discussed in the sections that follows :

4.1. Paracetamol (Acetaminophen)

It causes antipyresis by exerting its action on the **hypothalamic heat-regulating centre,** and analgesia by enhancing the pain threshold profile appreciably. It is found to lack the anti-inflammatory

*Clark WG, **Mechanisms of Antipyretic Action**, *Gen. Pharmacol.*, **10** : 71–77, 1979.

Hughes J and Kosterlitz, *Nature*, **258 : 577, 1975.

activity of the salicylates ; therefore, its therapeutic usefulness in inflammatory disorders is very much limited, and hence is not regarded as an NSAID agent. In contrast to the action of **'aspirin',** paracetamol possesses little affect in antagonizing the actions of uricosuric agents (*i.e.,* increases the urinary excretion of uric acid). It has also been observed that its large doses usually help in potentiating the action of the anticoagulants, whereas the normal therapeutic dose regimens exert hardly any effect on the **'prothrombin time'** (*i.e.,* coagulation time).

Nearly, 2% of the **'drug'** is excreted almost unchanged in the urine, while approximately 95% is found as its corresponding **glucuronide and sulphate-conjugates** that are absolutely devoid of any toxicity. Furthermore, the remaining 3% gets oxidized *via* the *hepatic cytochrome P-450 system* into a respective chemically reactive intermediate which eventually combines specifically with the **liver glutathione** to give rise to the formation of a **'nontoxic'** entity.

4.2. Phenacetin

Its toxic effects are very much comparable to those of **paracetamol (acetaminophen),** the '*active form*' to which it gets converted *in vivo.* The earlier findings revealed that it may cause a damage to the kidneys when used either in excessive dosage or for a longer duration. However, certain interesting recent evidences strongly suggest that phenacetin may *not* be responsible for causing nephritis to any greater extent when compared to **'aspirin'***. Importantly, it has been strongly demonstrated in causing carcinogenesis in rats and associated with the growth of tumours in abuses of **phenacetin****.

4.3. Acetanilide

It is considered to be relatively safer drug in the doses recommended for analgesia. Hence, it may be administered in intermittent periods, not exceeding a few days in any circumstances. The analgesic effect is quite selective for pharmacological action(s) ranging from simple headache to the pain associated with many muscles and joints.

4.4. Aspirin

It has been well established that **'aspirin'** inhibits platelet function ; therefore, it prophylactically minimises the incidence of **myocardial infarction** and **transient ischemic attacks** particularly in men and also postmenopausal women. Interestingly, **aspirin** is *not* hydrolyzed significantly when it happens to be in contact with the weakly acidic digestive juice present in the stomach (*i.e.,* gastric juice) ; however, as soon as it gains its passage into the intestinal canal it undergoes hydrolysis to a certain extent. A large portion of it usually gets absorbed unchanged. Garrett*** (1959) put forward a logical explanation with regard to the gastric mucosal irritation of aspirin to the formation of **salicylic acid** *i.e.,* the natural inherent acidity of **aspirin** ; besides, the intimate adhesion of undissolved **aspirin** to the gastric mucosa. Subsequently, Davenport**** (1967) demonstrated that **aspirin** affords an irreversible modification in the degree of permeability in the mucosal cell, thereby permitting the **'back-diffusion'** of gastric acid (in stomach) that ultimately is responsible in causing permanent damage to the capillaries.

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*Brown DM and Hardy TL., *Brit J. Pharmacol. Chemother.,* **32**, 17, 1968.

Tomatis L. *et. al. Cancer Res.* **38, 877, 1978.

***Garrett ER, *J. Am. Pharm. Assoc. Sci.,* **48**, 676, 1959.

****Davenport HW, *N. Engl. J. Med.,* **276**, 1307, 1967.

4.5. Sodium Salicylate

It is considered to be one of the **'choicest drug'** specifically for salicylate medication ; and is usually administered with either sodium bicarbonate to minimise effectively the **'gastric distress'** or as **enteric-coated dosage forms.** However, the usage of $NaHCO_3$ is not advisable as it is found to retard the plasma levels of **'salicylate'** and enhances the elimination of **'free salicylate'** in the urine.

4.6. Salicylamide

It is believed to exert a moderately faster and deeper analgesic effect in comparison to **'aspirin'**. It has also been established that its long term usage in rats no abnormal and untoward physiological and symptomatical reactions observed. Salicylamide gets metaboilized in a manner altogether different from that of other **'salicylates'** ; and, importantly it hardly gets hydrolyzed to the corresponding salicylic acid.*

4.7. Salsalate

The ester is usually hydrolyzed following its immediate systemic absorption. It is believed to afford much less gastric irritation and discomfort in comparison to **'aspirin'**, by virtue of the fact that the **'drug'** is virtually insoluble in the *stomach* ; and, therefore, never gets absorbed unless and until it happens to gain its access into the **small-intestine.** It is found to be as effective as **'aspirin'** and definitely possess fewer side effects.

4.8. Choline Salicylate

It is observed to be absorbed much more swiftly in comparison to **'aspirin',** thereby giving rise to faster peak blood levels.

4.9. Fluferisal

It is found to be more potent, long acting and possesses much less gastric irritation. All these characteristic features have been duly accomplished, by strategically introducing a hydrophobic functional moiety (4-fluorophenyl) at C-5. Just like other aryl acids the '**drug**' is most intimately bound to plasma proteins in the shape of its deacylated metabolite. However, in human beings it seems to be at least twice as effective *i.e.*, having almost twice the duration of activity.

4.10. Cinchophen

Its antipyretic actions are very much akin to those of the salicylates. Its major pharmacological action was in the control and management of **chronic gout and rheumatic** conditions, but by virtue of its relatively high level of toxic effects, such as : hepatic dysfunction ultimately leading to acute jaundice.

4.11. Phenazone (Antipyrine)

The drug is found to exert an appreciable paralytic action exclusively upon the sensory and the motor nerves which eventually give rise to certain degree of anaesthesia and vasoconstriction. Somatically (*i.e.*, systemically), it is observed to afford pharmacological activities which are very similar to those of **acetanilid** ; evidently these are normally quite fast and rapid. After due oral administration, it undergoes a free circulation within the system, and finally gets excreted through the kidneys in an **'unchanged form'**. It remarkably helps in reducing the abnormally high temperature in an exceptionally rapid man-

*Smith PK, *Ann. N.Y. Acad. Sci.*, **86**, 38, 1960.

ner *via* an altogether not-so-explicite (unknown) mechanism. Perhaps it is normally caused by a direct effect upon the **serotonin-regulated thermal controlling centre** of the nervous system. Besides, it remarkably minimises certain kinds of perception to pain, without any change in the prevailing central or motor functions, that essentially varies from the effects of **morphine**.

4.12. Aminopyrine

Though its overall antipyretic and analgesic effect is much more powerful and its effect last longer, yet it possesses a major disadvantage because of its ability to produce agranulocytosis* (granulocytopenia). It has been further demonstrated to be caused by drug therapy with a plethora of drug substances *e.g.*, **aminopyrine.**

Note. Several countries have either banned or adequately restricted its administration.

4.13. Dipyrone

Its pharmacological actions are very much akin to **aminopyrine**. Because of its high degree of toxicity its usage has been banned or restricted in several countries.

4.14. Phenylbutazone

The **'drug'** is absorbed quite rapid after oral administration, and subsequently gets bound to plasma protein very intimately. Its usual time to attain peak serum concentration level is nearly 2.5 hrs. However, the normal span for the overset of antigout activity ranges between 1 to 4 days, and that for antirheumatic activity varies between 3 to 7 days. It has been duly observed that the therapeutic serum concentrations average approximately 43 mg. mL^{-1} ; and the elimination half-life is nearly 84 hours. Interestingly, its major metabolite (oxyphenbutazone, 2%) and the unchanged drug (1%) are both excreted by the kidneys.

Note. The 'drug' must preferably be taken either with cold milk or with meals to avoid the possible gastric irritation.

4.15. Oxyphenbutazone

It happens to be the **'active metabolite'** of **phenylbutazone**. It has more or less the same effectiveness, side-effects, indications and contraindications. Undoubtedly, it affords a distinct less frequent incidence of acute gastric irritation.

4.16. Benorylate

The **acetaminophen (paracetamol)** ester of **aspirin**, **benorylate**, is an interestingly novel example of a prodrug where both the individual entities represent active agents. The **'drug'** seems to be free from the most undesirable **ulcerogenic characteristic features ;** and, therefore, soonafter the usual absorption, it gets split into its two active components once again by the aid of **serum esterases.** It has been duly reported to serve as an effective analgesic-anti-inflammatory drug.

4.17. Sulfinpyrazone

It belongs to the class of a pyrazone structural analogue having potent uricosuric activity together with some antirhombotic and platelet inhibitory activity. It is invariably employed to minimise **the serum-urate concentration** in the specific instances of chronic and intermittent gouty arthritis. It is ob-

*An acute disease marked by a deficit or absolute lack of granulocytic WBC (neutrophils, basophils, and eosinophils).

served to get adequately absorbed after the oral administration ; 98 to 99% is bound to plasma protein, plasma half-life is almost nearly 2.2 to 3 hours, and finally 50% of the administered '*drug substance*' is usually gets excreted practically unchanged in the urine.

4.18. Mefenamic Acid

The precise mechanism of action of this **'drug'** is assumed to be related to its ability to block **prostaglandin (PG) synthetase** almost completely. It has also been observed that it does not bear any relationship whatsoever with respect to partition coefficient, dissociation contant (pKa), and lipid-plasma distribution. Besides, there are several evidences in literature(s) with regard to its **anti-UV erythema activities,** and **antibradykinin activities*.** It definitely shows much decreased incidence of **gastrointestinal bleeding,** a prominent drawback of such drugs, when compared to **'aspirin'**.** Besides, it has been duly approved for the control and management of primary dysmenorrhea, that is believed to be caused by an overwhelming concentrations of endoperoxides as well as prostaglandins (PG).

4.19. Meclofenamate Sodium

This is the 2, 6-dichloro derivative of mefenamic acid, as its sodium salt ; and exerts its most predominant side effects, such as : diarrhea, and gastro intestinal disorders.

4.20. Flufenamic Acid

It is a trifluoromethyl analogue of anthranilic acid, that exerts its three-in-one pharmacological actions *viz.*, antipyretic, analgesic, and anti-inflammatory. It finds its abundant usage in dysmenorrhoea and various types of rheumatic disorders. However, the exact and precise mechanism of antipyretic action of the N-aryl anthranilic acid structural variants has not yet been established. There exists no relationship to lipid plasma distribution, partition coefficient or pKa values of these types of drugs *vis-a-vis* their antipyretic activity.

Probable Questions for B. Pharm. Examinations

1. Classify the **'febrifuges'** and give the structure, chemical name and uses of at least ONE compound from each category.
2. Give the names of **three** drugs belonging to the category of **'aniline and para aminophenol analogues'.** Discuss the synthesis of **one** of them.
3. Discuss **'Salicylic Acid Analogues'** as potent antipyretic analgesics. Give suitable examples of support your answer.
4. What is the structure difference between **Cinchophen** and **Neocinchophen ?** Give the synthesis of any **one** of them.
5. The metabolite of **Phenylbutazone** is a better effecitve drug. Discuss its synthesis and is important uses.
6. Name a Sulphur containing **pyrazolodione drug** used as an antipyretic analgesic and describe its synthesis.

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*Scherrer RA, In : Scherrer RA and Whitehouse MW (eds.) **Antiinflammatory Agents**, Academic Press, New York, *p*-132, 1974.

Lane AZ *et al*, *J. New Drugs.*, **4, 333, 1964.

7. 'Structural analogues of N-arylanthranilic acid yielded some potent antipyretic, analgesic and anti-inflammatory compounds'. Justify the statement with **two** important examples along with their synthesis.

8. Discuss the **'mode of action'** of antipyretic analgesics by citing the examples of some typical drugs, which you have studied.

9. What are Salol, Partial Salol and True Salol ? Give the structure, chemical name and uses of **one** typical examples from each type.

10. Give a comprehensive account of **antipyretic-analgesics**.

RECOMMENDED READINGS

1. A Gringauz, **Introduction to Medicinal Chemistry,** Wiley-VCH, New York, (1997).
2. CO Wilson, O Gisvold and FR Doerge, **Textbook of Organic Medicinal and Pharmaceutical Chemistry,** (11th edn.) JB Lippincott Company Philadelphia (2002).
3. D Lednicer and LA Mitscher **The Organic Chemistry of Drug Synthesis,** John Wiley and Sons New York (1995).
4. HC Churchill-Davidson, **Hypothermia,** *Anaesth* June (1954).
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6. ME Wolff (ed.) **Burger's Medicinal Chemistry and Drug Discovery** (5th edn) John Wiley & Sons, New York (1995).
7. PAJ Janssen and CAM van der Eycken in : A. Burger (ed.) **Drugs Affecting the Central Nervous System,** Marcell Dekker, New York (1968).
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Chapter

11

Narcotic Analgesics (Opiate Analgesics)

1. INTRODUCTION

Opium was known to man many centuries ago. This is evident from the **Ebers Papyrus** and **Homer's Odyessey** where the use of opium was mentioned. Opium is obtained by making superficial incisions on the immature and unripe capsules of *Papaver somniferum* (or **poppy plant**). The exudate is air-dried and then powdered to give the official powdered opium. A systematic study of the plant material led to the isolation and identification of the most important alkaloid known as morphine in 1803. Other alkaloids isolated from opium include **codeine, papaverine and thebaine.**

The opium class of narcotic drugs are considered not only as the most potent and clinically useful agents causing depression of central nervous system, but also as very strong analgesics. **Morphine** and **morphine-like drugs** are referred to as **opioids** or **opiates**. They are also known as **narcotic analgesics** (**'narcotic'** is derived from the Greek word **'narcotic'** meaning drowsiness. The term **narcotic** is now used to refer to dependence producing drugs.

Morphine possesses a host of diverse pharmacological properties and uses, a few of which are, to check diarrhoea, ease dyspnea, suppress cough and above all, to induce sleep in the presence of pain. Though **morphine** and **morphine-like drugs** may not alter the sensation of pain but they modify the emotional reaction to pain. The pain may be present but may not be perceived as painful.

The narcotic analgesics tend to produce euphoria which is an important factor in their addictive property which limits their use. Other limitations include : *respiratory depression, decreased gastrointestinal motility leading to constipation, increase biliary tract pressure and pruritus due to histamine release.* Because of these setbacks in the use of morphine there has been a constant effort to develop analgesics with fewer side-effects and minimal addictive actions.

As on date a plethora of **CNS-depressants,** such as : **anti-psychotics, barbiturates** and **ethanol** have been shown to afford effectively a substantial lowering in the **'pain perception'.** It has been already demonstrated beyond any reasonable doubt that two vital phenomenon taking place *in vivo*, namely : (*a*) **norepinephrine** re-uptake (*viz.*, antidepressant drugs) ; and (*b*) preventors of **serotonin*** are extremely beneficial therapeutically when administered either in conjunction (adjuvant) with **'opiates'** or alone in the control and management of certain typical incidences of chronic pain.

*A chemical, **5-hydroxy tryptamine (5-HT)**, present in platelets, gastro intestinal mucosa, mast cells, and carcinoid tumours. It is a potent vasoconstrictor ; and also a neurotransmitter in the CNS, and is important in sleep-walking cycles.

With the advent of **'new mechanisms'** emphatically based on latest trend of research activities geared into the antinociceptive effects of certain centrally acting **cannabinoid, α-adrenergic-,** and above all the **nicotinic-receptor agonists** may ultimately give rise to a host of therapeutically potent and efficacious analgesics. Besides, basic fundamental research conducted with inhibitors to tachykinin (neurokinin) receptors evidently shows adequate promising results leading to the discovery of newer breed of analgesic drug substances into the therapeutic armamentarium. It is, however, pertinent to state at this juncture that while the constant efforts are still on with respect to the evolution of **'new-drugs'** the **chronic** as well as **acute pain** is invariably circumvented with the aid of **'opioid analgesics'** most efficaciously.

2. LIMITATIONS OF OPIATE ANALGESICS

There are several disadvantages as well as limitations of **'opiate analgesics'** that are enumerated as under :

(*a*) these are usually *contraindicated* in patients who have essentially a past record of Addison's disease, myxedema, and hepatic cirrhosis.

(*b*) these **'drugs'** exhibit a tendency of minimising ventilation that ultimately give rise to hypercapnia and lead to cerebrovascular dilatation resulting into enhanced intracranial pressure ; therefore, great caution has got to be observed in such situations (conditions) as : cerebral edema, head injuries, and delerium tremens.

(*c*) these are required to be used with utmost caution and restriction in patients having a history of cardiac arrythmias, inpaired kidney function, and chronic ulcerative colitis.

(*d*) these **'drugs'** have a tendency to cross the **placental barrier** ; therefore, newborn infants, whose mothers have been treated with such drugs during labour, must be observed very meticulously for probable symptoms of **respiratory depression,** and should be treated adequately for narcotic overdosage, if so required.

(*e*) an individual who is sensitive either to a specific narcotic agent or a group of agents, must avoid them as far as possible to get into serious complications that may even prove fatal.

(*f*) these '*drugs*' invariably exhibit amalgamated **'analgesic'** and **'depressant'** effects that form the basis for a large number of **drug-drug interactions** with other therapeutic agents.

Examples : (1) A plethora of **'drug substances',** for instance : muscle relaxants, sedatives-hypnotics, tricyclic antidepressants, antipsychotic, antihistaminics, and alcohols are observed to interact with **opiate analgesics** to augment and accelerate their overlapping pharmacological activities, namely : anticholinergic effects and respiratory depression.

(2) **Monoamine oxidase inhibitors (MAOIs)** must be administered with utmost caution in conjunction with **'narcotic analgesics'** by virtue of their extremely intensified activity, for instance : patients treated with MAOIs when treated with '**meperidine**' give rise to such a severe reaction that may sometimes even prove to be fatal.

In short, one may infer from the aforesaid statement of facts (*a*) through (*f*) that the **'opiate analgesics'** on one hand produce wonderful much needed therapeutic excellence, but on the other extreme care, caution and wisdom need to be applied in their usage in treating specific conditions.

3. CHARACTERISTIC FEATURES OF OPIOIDS

There are several specific characteristic features of **opioids (opiates)** as detailed below which would be treated individually here under :

(*i*) Opioid peptides,

(*ii*) Opioid receptors,

(*iii*) Orphan opioid receptor,

(*iv*) Mu opioid receptors,

(*v*) Kappa opioid receptors,

(*vi*) Delta opioid receptors, and

(*vii*) Opioid receptors : identification and activation.

3.1. Opioid Peptides

Akil *et al*., (1984) observed that the **endogenous opioid peptides** are invariably synthesized as essential component associated with the structures of specific large precursor proteins. Evidently, each of the major types of opioid peptides does have an altogether different and specific precursor protein.

Examples :	**Opioid Peptide**	**Precursor**
(*i*)	**Proenkephalin A**	— Met- and Leu-Enkephalin
(*ii*)	**Propiomelanocortin (PMOC)**	— β-Endorphin
(*iii*)	**Proenkephalin B (Prodynorphin)**	— Dynorphin, and α-Neoendorphin

Salient Features. The various salient features of the **opioid peptides** are stated as under :

(1) Most of the **pro-opioid proteins** are usually synthesized very much within the cell nucleus, and subsequently transported meticulously to the terminals of the nerve cells from where they are being released gradually.

(2) Active peptides are found to be undergoing hydrolysis from the corresponding large proteins by the aid of proteases which particularly, take cognizance of the **'double basic amino acid sequences'** strategically located just prior and immediately after the opioid peptide sequences.

(3) **Endogenous opioid peptides** are found to afford their analgesic activity both at the supraspinal and spinal sites :

(*a*) Cause analgesia alternatively by the help of a peripheral mechanism of action intimately linked with the pervailing inflammatory process, and

(*b*) CNS-happens to be the ideal most preferred site where the opioids are found to exert either a neuromodulator or an inhibitory neurotransmitter action at the following *two* prevalent sites, namely :

(*i*) interconnecting neuronal pathways meant for the exclusive **'pain signals'** within the brain, and

(*ii*) afferent pain signalling neurons located in the dorsal horn of the spinal cord.

3.2. Opioid Receptors

Generally, there exist *three* main categories of the '*opioid receptors*', namely : (*a*) mu ; (*b*) kappa designated by '*k*' ; and (*c*) delta designated by 'δ'.* It is, however, pertinent to state here that all the aforesaid opioid receptors have been adequately characterized and also '*cloned*'.** Based on the most recent universally adopted and recognized **'nomenclature'** classifies the said three opioid receptors in the actual order by which they were eventually cloned.*** According to this classification the various receptors are commonly termed as follows :

OP_1—Receptors : Delta opioid receptors (δ) ;

OP_2—Receptors : Kappa opioid receptors (κ) ;

OP_3—Receptors : mu opioid receptors ;

Interestingly, all the three **'opioid receptor types'** are found to be strategically located either in the human brain or spinal cord tissues ; furthermore, each of them essentially possesses a specific role to play in the control, regulation and management of pain threshold. As on date, however, both **mu** and **kappa** agonists are already in clinical application abundantly across the globe ; whereas, a good number of **delta receptor** selective drug substances are in the regimen of both extensive and intensive **'clinical trial procedures'.**

3.3. Orphan Opioid Receptor

Importantly, an absolutely different 4th receptor, besides mu-delta-kappa opioid receptors, has been duly identified and cloned derived from the homology with the cDNA sequence of the known ones. One of the most predominant feature of the new 4th receptor is that it never got bound to the classical opioid peptide or prevailing antagonists or known non-peptide agonists with high affinity. Therefore, this new receptor has been legitimately termed as the **orphan opioid receptor**. Inspite of the copious volume of research carried out to establish the exact mechanism of this receptor no definite experimental evidence(s) to suggest adequately the importance of this system with respect to the pain transmission and its prevailing association to the classical opioid systems.

3.4. Mu Opioid Receptors

Zadina *et al.***** (1997) made a pivotal observation that the *two* vital **endogenous opioid peptides,** namely : (*a*) **endomorphin-1** ; and (*b*) **endomorphin-2.** showed an extremely high degree of selectivity for the mu (OP_3) receptors exclusively.

Salient Features. The salient features of **mu opioid receptors** are as follows :

1. A plethora of therapeutically potent and useful compounds, such as : **morphine, sufetanil, ndomorphin-1, ndomorphin-2, are potent Mu (μ) opioid agonists.**
2. A number of other pharmacologically active compounds, for instance : **Naloxone, Cyprodime, Naltrexone are Mu (μ) opioid antagonists.**
3. Practically all the **'opioid alkaloids'** and most of their synthetic structural analogues are precisely the mu selective agonists.

*Lord JAH *et al.* **Endogenous opioid peptides : multiple agonists and receptors,** *Nature,* **267** : 495-499, 1977.

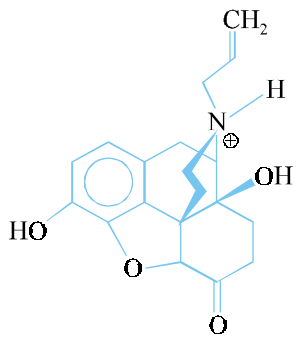
Satoh and Minami, **Molecular pharmacology of the opioid receptors, *Pharmacol. Ther.*, **68,** 343-64, 1995.

***Dhawan BN *et al. Pharmacol. Rev.*, **48**, 567-592, 1996.

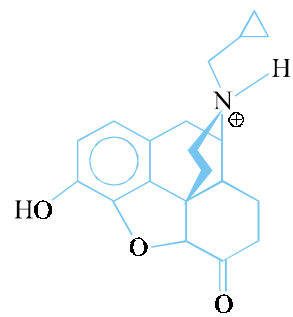
****Zadina JE *et al. Nature*, **386 :** 499-502, 1997.

4. Three **'drug substances',** namely : **morphine, normorphine,** and **dihydromorphinone** are found to have 10–20 times more **mu receptor** selectivity.
5. Kieffer* (1999) amply demonstrated that almost all the major pharmacologic activities, as studied **with mu receptor knockout mice,** after having been treated with morphine injection usually take place by interactions with mu receptors. Such observed activities are : decreased gastric motility, emesis, tolerance, analgesia, respiratory depression and withdrawl symptoms.
6. **Cyprodime** happens to be the most selective non-peptide mu antagonist *i.e.*, showing 100 time more selectivity for mu over delta ; and 30 times more selectivity for mu over kappa.
7. **Naltrexone** and **Naloxone** are recognized as opioid antagonists which exhibit only negligible *i.e.*, 5 to 10 fold more selectivity for the mu receptors.

SAR-Mu Antagonists. It has been observed that there are only *two* drug substances which are recognized as **'pure antagonists'** *i.e.*, they behave as antagonists at all opioid receptor sites, such as : **naloxone** (*i.e.*, N-allyl) ; and **naltrexone** (*i.e.*, N-cyclopropylmethyl) structural analogues of **noroxymorphone.** The 14β-OH functional moiety is regarded to be the most important characteristic feature for attributing the pure antagonistic properties of these two aforesaid compounds.



Naloxone



Naltrexone

However, it has not yet been expatiated completely as to why a minor alteration from an N-methyl to an N-allyl moiety can reverse the activity of **'an opioid'** from being a **potent agonist** into a **potent antagonist**. Perhaps a logical explanation may be put forward with regard to the capability of opioid receptor protein to couple with **G-proteins**** efficaciously in the event when it got bound by an agonist but no such coupling with **G-proteins** when got bound by an antagonist. Furthermore, one may draw an inference that in the instance of an opioid with an N-substituent of 3-4 carbon number, exerts a distinct conformational change either in the receptor or blocks essential receptor areas that might specifically hinder the possible interaction between the receptor and the **G-proteins.**

3.5. Kappa Opioid Receptors

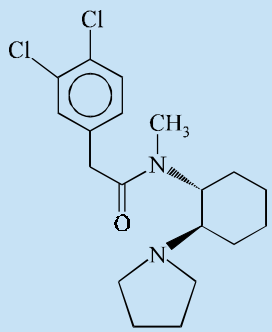
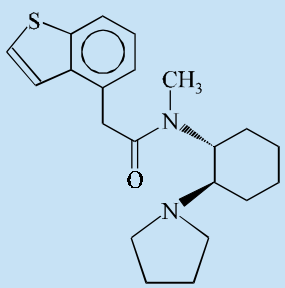
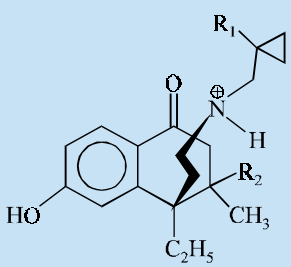
The two prominent 6, 7-benzomorphan structural analogues are the racemate of **ethylketazocine** and **bremazocine** which predominantly exhibit **kappa opioid receptor** selectivity. These two compounds gained prominence as they were used initially to evaluate the **kappa receptors** ; but later on found to be possessing not-so-high a selectivity. However, quite recently, a variety **'arylacetamide'**

*Kieffer BL, *Pharmacol, Sci.*, **20**, 19-25, 1999.

**Signal transduction proteins.

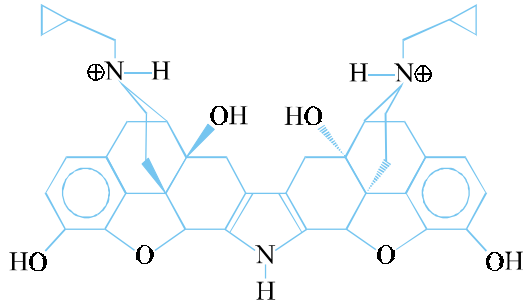
structural analogues, which showed a distinctly higher selectivity for kappa in comparison to mu or delta receptors, have seen the light of the day. The *two* new racemic compounds investigated largely are : U50488 and PD117302, whose characteristic features along with the earlier ones are enumerated in Table 10.1.

Table 11.1 : Characteristic Features of Kappa (κ) Opioid Agonists

S. No.	Racemate Compounds	Characteristic Features
1.	**(±)-U50488** 	1. It shows 50 times more selectivity for kappa over mu receptors. 2. It enjoys the reputation of being the most-important '*pharmacological tool*' in the characterization of the kappa opioid activity solely.
2.	**(±)-PD117302** 	1. It exhibits almost 1000 times selectivity for kappa over mu or delta receptors. 2. Generally, the kappa agonists cause distinct analgesia in humans and animals.
3.	**(±)-Ethylketazocine [R_1 = H ; R_2 = H]** **(±)-Bremazocine [R_1 = OH ; R_2 = CH_3]** 	1. Used earlier to help in the investigational studies with regard to kappa receptors. 2. Not found to be possessing enough sensitivity and selectivity ; and hence, replaced by U-50488 and PD-117302 (*i.e.*, the *arylacetamides*).

In the search for **kappa (κ) opioid antagonists** only one drug substance gained cognizance, which is **(±) nor-binaltorphimine,** and it showed fairly good selectivity for the kappa receptors.*

*Choi H *et. al., J Med. Chem.*, **35** : 4638-39, 1992.



(±) nor-Binaltorphimine

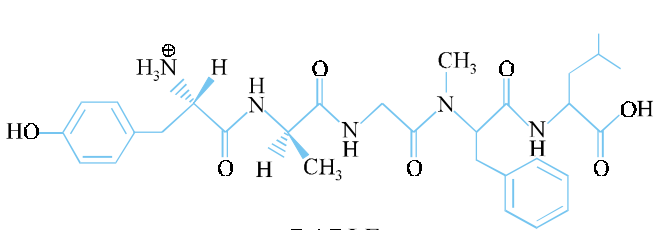
SAR-Kappa Receptor Agonists. Most of the clinically used kappa agonists essentially have their chemical structures very much related to the rather '**rigid opioids**', and those having the additional functional moieties attached to the N-atom, such as : **allyl ; cyclopropylmethyl (CPM)** ; and **cyclobutylmethyl (CBM).** Interestingly, all these compounds are observed to be **kappa receptor agonists ;** besides being **mu receptor antagonists**. Importantly, the **kappa agonist** activity may be increased substantially by the following *two* minor structural modifications as stated under :

(*a*) introduction of the O-atom placed strategically at the 8-position [*e.g.*, **ethylketazocine** (Table 11.1)], and

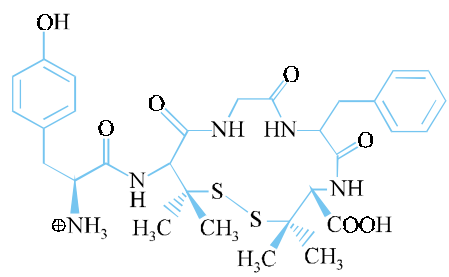
(*b*) introduction of the O-atom right into the N-substituent [*e.g.*, **bremazocine** (Table 11.1)].

3.6. Delta Opioid Receptors

Adequate modifications and alterations in the amino-acid sequence and composition of the **enkephalins** (pentapeptides produced in the brain) give rise to such compounds that significantly demonstrate both high potency and distinct selectivity for the delta opioid receptors. James *et. al.** (1984) introduced **[D-Ala^2, D-Leu^5] enkephalin,** also termed as **DADLE ;** whereas, Mosberg *et al.*** (1983) introduced the cyclic peptide **[D-Pen^2, D-Pen^5] enkephalin,** also known as **DPDPE,** which enjoyed the reputation of being the peptides invariably and frequently employed as **selective delta receptor ligands.**



DADLE



DPDPE

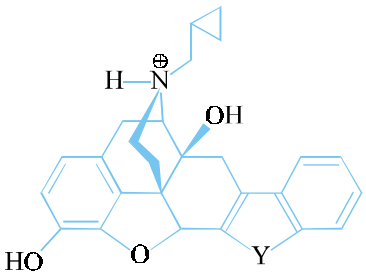
Both **DADLE** and **DPDPE** together with some other **delta-receptor-selective peptides** have been employed extensively and intensively for carrying out numerous *in vitro* studies initially. Based on

*James IF *et al., Mol. Pharmacol.*, **25** : 337-342, 1984.

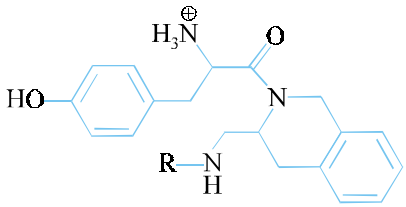
Moseberg HI *et al., Proc Natl Acad Sci* USA, **80 : 5871-4, 1983.

their two cardinal characteristic negative qualifications, namely : (*a*) metabolic instability ; and (*b*) poor distribution properties*, their overall usefulness for *in vivo* studies have been restricted immensely.

Takemori *et al.*** (1992) introduced *two* highly selective nonpeptide delta (OP_1) opioid antagonists for the delta receptors exclusively, as illustrated below : *i.e.*, **naltrindol,** and **naltiben.**



Naltrindol, Y = NH ;
Naltiben, Y = O ;



Tipp : R =

Tipp – ψ : R = OH

Of the two compounds stated above the former is observed to penetrate the CNS and shows antagonist activity which is particularly selective for the delta (OP_1) receptors both *in vitro* and *in vivo* systems.

Schiller *et al.**** (1993) reported **two peptidyl antagonists TIPP and TIPP-Ψ,** as shown above which are found to be selective for **delta receptors.** Unfortunately, their clinical usefulness as well as their ability to give fruitful results for *in vivo* studies have been virtually jeopardized and negated by virtue of their absolutely poor pharmacokinetic characteristics.

Interestingly, the **opioid receptor** antagonists have surprisingly demonstrated appreciable clinical potential both in the treatment of cocaine abuse, and as an immuno suppressive agent.

SAR-Delta Receptor Agonists. The various cardinal factors with respect to the SAR of delta receptor agonists are enumerated as under :

- SARs for the delta receptor agonists have been least explored/investigated amongst the **'opioid drugs'.**
- **Naltrindol** and naltiben *i.e.*, the two **nonpeptide delta selective agonists,** are picking up investigative interest gradually.
- Peptides having high selectivity for delta receptors are already established and documented.
- Number of selective delta agonists are very much still under the required **'clinical trials',** and may be approved as a potential **'drug substance'** of the future.

3.7. Opioid Receptors : Identification and Activation

The identification of **'multiple opioid receptors'** has been adequately accomplished with the subsequent discovery of certain selective potential agonists as well as antagonists ; and the *two* most sophisticated and reliable '**assay methods**' as given below :

*Penetration into the blood-brain.

Takemori *et al. Life Sci.*, **149 : 1–5, 1992.

***Schiller PW *et al. J. Med. Chem.*, **36** : 3182-7, 1993.

(*a*) **Leslie's Method* (1987).** For the identification of sensitive assay techniques, and

(*b*) **Satoh and Minami's Method** (1995).** For the ultimate cloning of the receptor proteins.

Salient Features. The various salient features with respect to the identification and activation of the **'opioid receptors'** are, namely :

(1) Two techniques are used predominantly, such as : (*a*) the radioligand binding assays on the brain-tissues ; and (*b*) the electrically stimulated peripheral muscle preparations.

(2) To differentiate the **'receptor selectivity'** of test compounds the following specific assay procedures may be adopted :

(*a*) computer aided line-filling, and

(*b*) selective blocking by using either reversible or irreversible binding agents with certain types of receptors.

(3) Signal transduction mechanism for mu, delta, and kappa receptors is *via* the **Gi/o proteins.** Thus, the activation of the ensuing opioid receptors is directly associated with the G protein to an inhibition of the critical **adenylate cylase activity.** Consequently, the ultimate lowering in cAMP production essentially affords an efflux of k^+ ions, and finally gives rise to **hyperpolarization of the nerve cell.*****

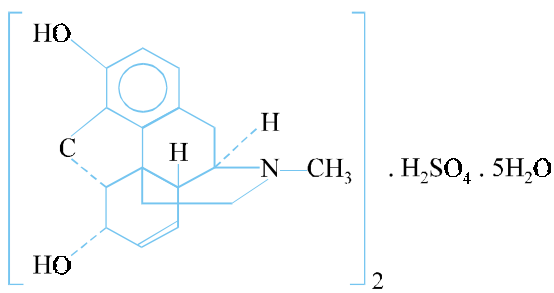
4. CLASSIFICATION

The narcotic analgesics are usually classified on the basis of their basic chemical structures as discussed below along with a few classical examples from each category.

4.1. Morphine Analogues

Morphine and related drugs possessing potent narcotic analgesic properties, are used in clinical practice. A few examples belonging to this class of compounds are morphine sulphate ; **diamorphine hydrochloride ; codeine ; dihydrocodeine phosphate ; hydromorphone hydrochloride ; hydrocodone tartrate ; oxymorphone hydrochloride.**

A. Morphine Sulphate BAN, Morphine Sulfate USAN.



7, 8-Didehydro-4, 5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2 : 1) (salt) pentahydrate ; Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2 : 1) (salt), pentahydrate ; B.P., U.S.P., Int. P., Ind. P ; Duraphine(R) (Elkins-Sinn).

*Leslie FM, *Pharmacol. Rev.*, **39,** 197–249, 1987.

Satoh M and Minami M., *Pharmacol. Ther.*, **68, 343-64, 1995.

***Childers SR, *Life Sci.*, **48**, 1991–2003, 1991 ; Georgoussi *et al. Biochem. J.*, **306,** 71-5, 1995.

Preparation

Morphine can be prepared by total synthesis, but due to the complexity of the molecule renders such an approach not viable commercially. Even today the main bulk of morphine is derived from the natural source and various analogues prepared therefrom.

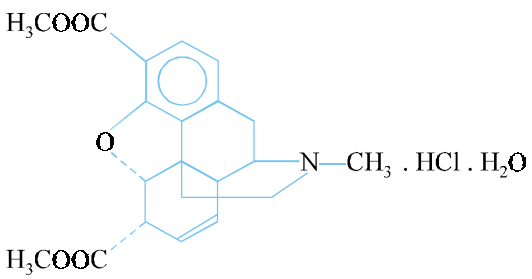
Method-I. The aqueous extract after concentration is neutralized, a solution of calcium chloride is now added, and the resulting mixture is filtered and further concentrated. The crude morphine hydrochloride separates out and is purified by precipitation with ammonia and recrystallised finally as the sulphate.

Method-II. The concentrated aqueous extract is mixed with ethanol and made sufficiently alkaline with ammonia, when morphine being sparingly soluble in dilute ethanol separates out while the remaining alkaloids are left in solution. The crude **morphine** thus obtained is usually purified by repeated crystallization as the corresponding sulphate.

It is employed extensively as an analgesic, antitussive, adjunct to anaesthesia and nonspecific antidiarrheal agent. In small doses it helps to alleviate continued dull pain, wheras in large doses to relieve acute pain of traumatic or visceral origin. **Morphine** is responsible for altering the psychological response to pain and thereby suppresses anxiety and apprehension, and enables the subject to be more tolerant to discomfort and pain. It is specifically used in the **management of postoperative pain and also for alleviating pre-operative apprehension.**

Dose : *Usual, adult, oral, 10 to 30 mg 6 times daily.*

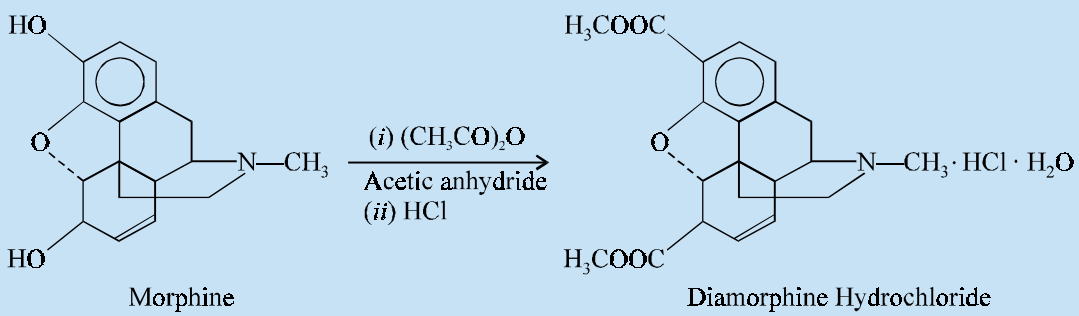
B. Diamorphine Hydrochloride BAN, Diacetylmorphine Hydrochloride USAN.



3, 6-*o*-Diacetylmorphine hydrochloride monohydrate ; Heroin Hydrochloride ; Diamorphine Hydrochloride B.P., Diacetylmorphine Hydrochloride U.S.P. IX ;

Diamorphine(R) (Roche, U.K.)

Synthesis



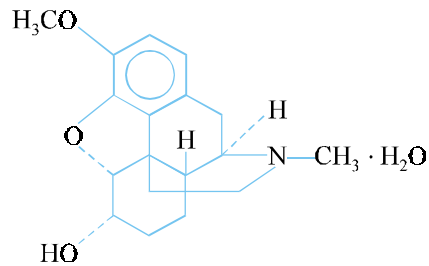
Morphine Diamorphine Hydrochloride

It may be prepared by the acetylation of **morphine** and subsequent treatment with hydrochloric acid.

Diamorphine hydrochloride possesses similar actions to that of **morphine**. It is found to be a more potent analgesic than **morphine** but it has a shorter duration of action stretching up to 3 hours only. It is generally *employed for the relief of severe pain particularly in terminal illnesses.* Used pre- and post-operatively and being a strong addictive, diamorphine is rigidly controlled and not available in international market.

Dose : *Oral, subcutaneous, intramuscular, 5 to 10 mg.*

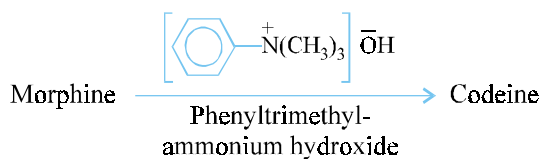
C. Codeine BAN, USAN,



7, 8-Didehydro-5, 5α-epoxy-3-methoxy-17-methyl-morphinan-6α-ol mono-hydrate ; Morphinan-6-ol, 7, 8-didehydro-4, 5-epoxy-3-methoxy-17-methyl-, monohydrate ; B.P., U.S.P., Eur., P., Int. P.

Synthesis

The consumption of codeine is much more than morphine and hence it may be prepared by the partial synthesis of **morphine** as stated below :

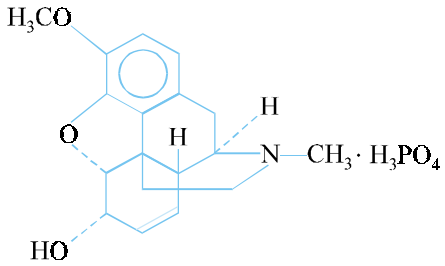


One of the phenolic OH groups in **morphine** is methylated by phenyltrimethyl ammonium hydroxide. The process involves dissolution of **morphine** in a solution of KOH in absolute alcohol along with the appropriate quantity of the methylating agent and the resulting solution warmed to 130°C. Afer cooling, water is added and the remaining solution is acidified with sulphuric acid. The generated dimethylaniline is separated and the excess of alcohol is removed by distillation under reduced pressure. The codeine is precipitated by the addition of sodium hydroxide and may be purified by crystallization as the sulphate salt.

It is a narcotic analgesic with utilities similar to those of **morphine,** but its analgesic activity is relatively much less. It exhibits only mild sedative effects.

Dose : *Usual, adult, oral, analgesic, 30 mg 6 times a day ; as antitussive, 5 to 10 mg every 4 hours.*

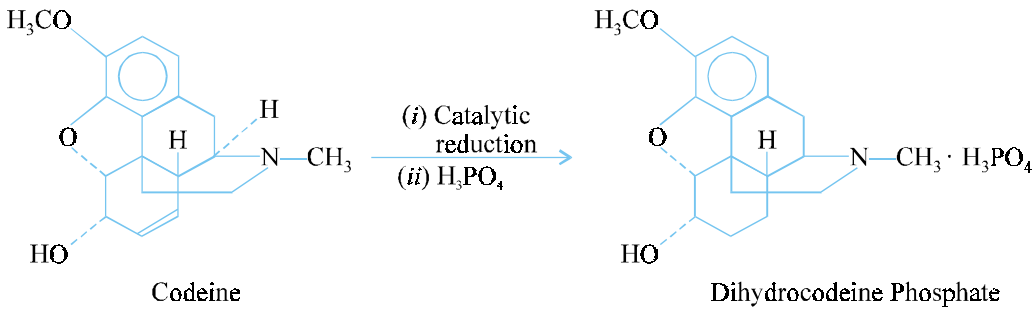
D. Dihydrocodeine Phosphate BAN, Dihydrocodeine INN, Drocode USAN,



7, 8-Dihydrocodeine phosphate ; Hydrocodeine Phosphate ; Jap. P.,
Rapocodin(R) (Knoll)

Synthesis

It may be prepared by the catalytic reduction of codeine and treating the resulting product with phosphoric acid.

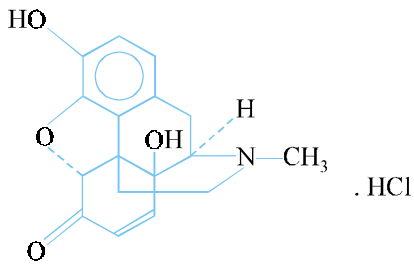


Codeine Dihydrocodeine Phosphate

It is used for the relief of mild to moderate pain.

Dose : *Usual, oral, 30 mg 4 to 6 times a day.*

E. Hydromorphone Hydrochloride BAN, USAN, Hydromorphone INN.



4, 5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride ; Morphinan-6-one, 4, 5-epoxy-3-hydroxy-17-methyl-, hydrochloride, (5α)- ; Dihydromorphinone Hydrochloride ; U.S.P., Int. P.,
Dilaudid(R) (Knoll) ;

Synthesis

Method-I ; From Morphine

$$\text{Morphine} \xrightarrow[(ii)\ \text{Reaction with HCl}]{(i)\ \text{Reduction}} \text{Hydromorphone Hydrochloride}$$

It may be prepared by the reduction of morphine and then treating the resulting product with an equimolar quantity of hyrochloric acid.

Method-II : From Dihydromorphine

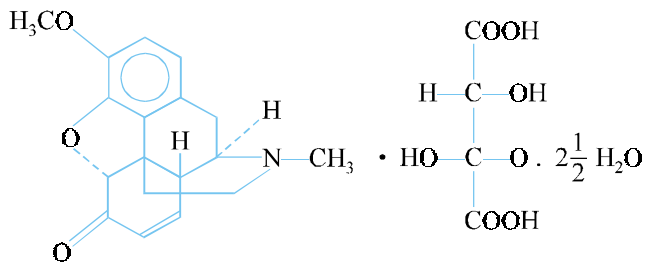
$$\text{Dihydromorphine} \xrightarrow[(ii)\ \text{Reaction with HCl}]{(i)\ \text{Oxidation}} \text{Hydromorphone Hydrochloride}$$

It is prepared by the oxidation of **dihydromorphine** and then reacting with an appropriate amount of hydrochloric acid.

It is a semisynthetic opiate analgesic, similar in action to that of morphine, normally used in the *treatment and subsequent relief of mild to severe pain due to cancer, trauma, myocardial infarction, biliary and renal colic, post-operative pain and severe burns.* It is more potent than morphine and the analgesic effect commences within 15 minutes and lasts for about 5 hours.

Dose : *Subcutaneous and oral, 1 to 1.5 mg ; Usual, 2 mg every 4 hours.*

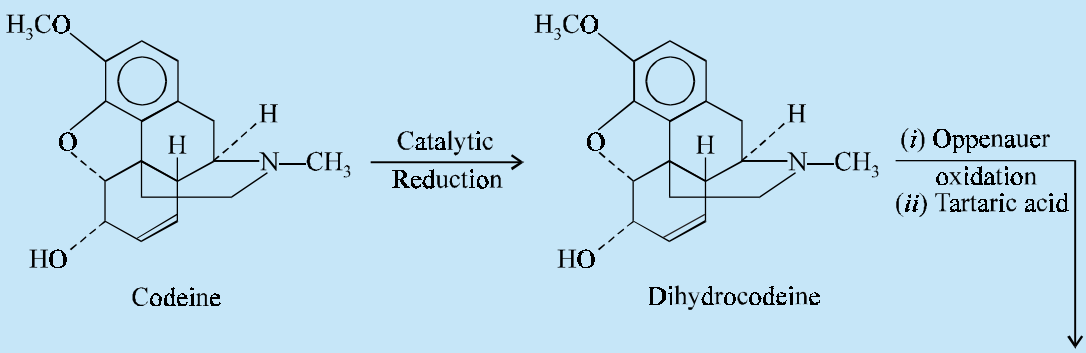
F. Hydrocodone Tartrate BAN, Hydrocodone Bitartrate USAN, Hydrocodone INN,



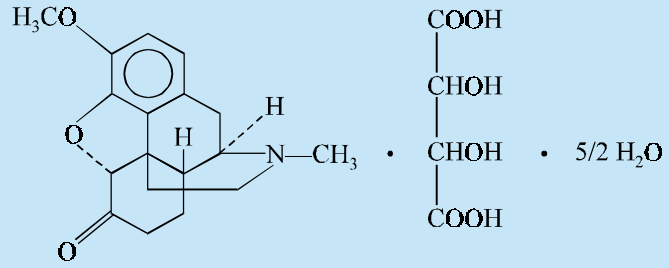
4, 5α-Epoxy-3-methoxy-17-methylmorphinan-6-one, tartrate (1 : 1) hydrate (2 : 5) ; Morphinan-6-one 4, 5-epoxy-3-methoxy-17-methyl-, (5α)-, [*R*-(*R**, *R**)]-2, 3-dihydroxybutanedioate (1 : 1), hydrate (2 : 5), U.S.P., Int. P.,

Dicodid(R) (Knoll) ; Mercodinone(R) (Merrell Dow)

Synthesis



(*Contd...*)



Hydrocodone Tartrate

It may be prepared by the catalytic reduction of codeine to yield **dihydrocodeine** which on being subjected to **Oppenauer oxidation** and treatment with equimolar quantity of tartaric acid gives rise to **hydrocodone tartrate.**

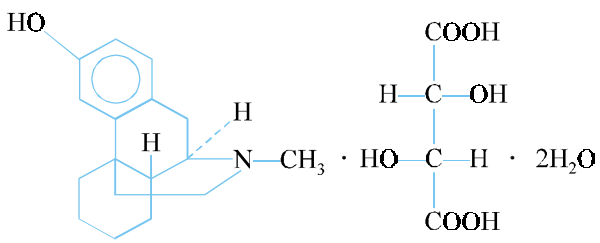
It is mostly used for the *relief of moderate to severe pain and also for the symptomatic treatment of cough.* It is a narcotic analgesic and considered to be more addictive than codeine.

Dose : *Usual, adult, oral, 5 to 50 mg per day.*

4.2. Morphinan Analogues

Grewe (1946) introduced a vital alkylation reaction *via* a very specific **stereo-selective** *(trans)* **synthesis** followed by acid-catalyzed intramolecular, aromatic substitution, which caused the B/C-*cis* C/D-*trans* ring fusions found to be common in either morphine or its natural congeners. This study has paved the way for an altogether new morphinan analogues known as **'benzomorphans'**. A few classical examples of this group of compounds are listed below, *viz.,* **levorphanol tartrate ; dextromethorphan hydrobromide ; butorphanol tartrate ;**

A. Levorphanol Tartrate BAN, USAN, s INN.



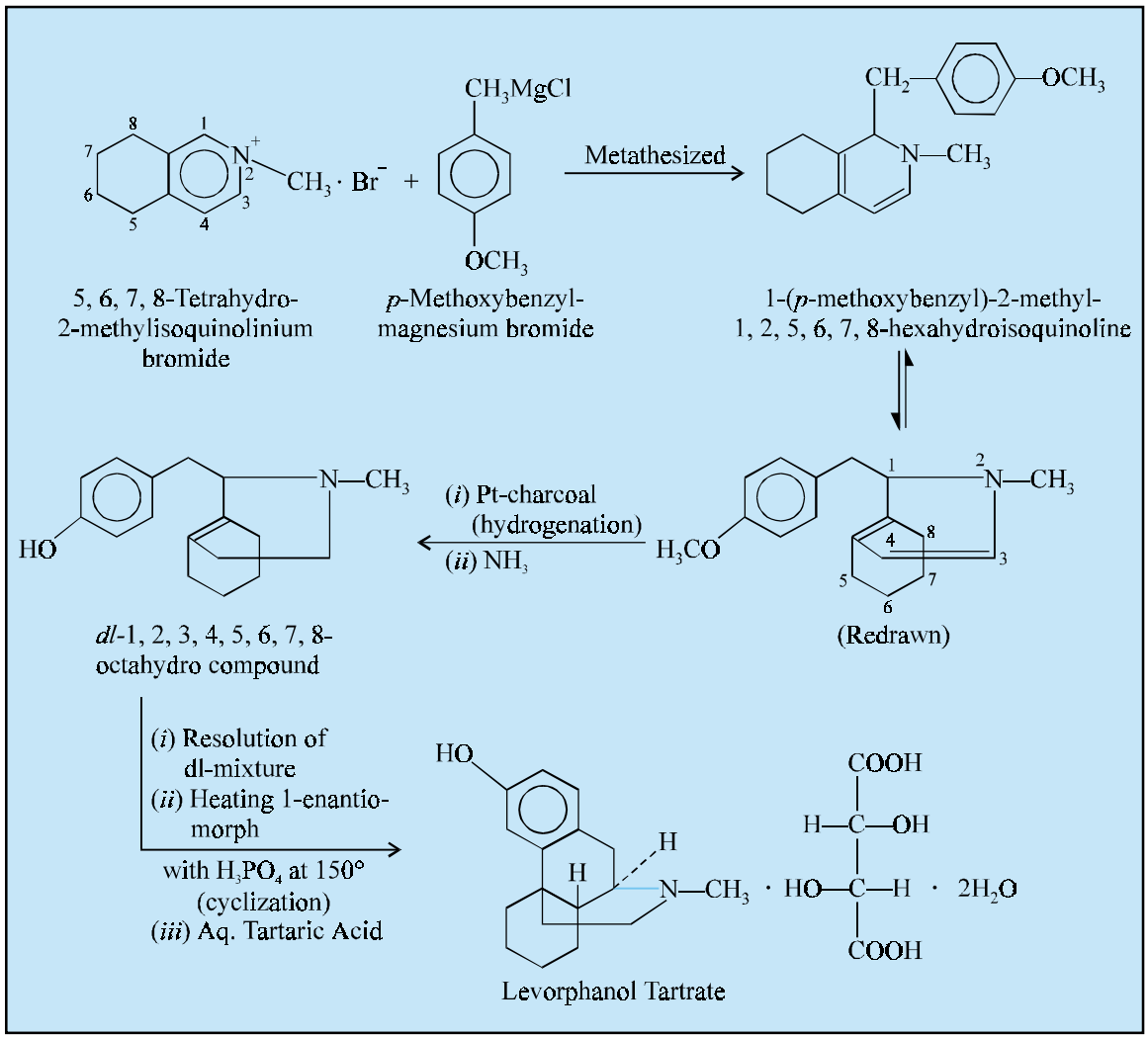
17-Methylmorphinan-3-ol, tartrate (1 : 1) (salt) dihydrate ; Morphinan-3-ol, 17-methyl-, (R-*R**, *R**]-2, 3-dihydroxybutane-diotate (1 : 1) (salt) dihydrate ; B.P., U.S.P.,

Levo-Dromoran(R) (Roche)

Synthesis

1-(*p*-Methoxybenzyl)-2-methyl-1, 2, 5, 6, 7, 8-hexahydroisoquinoline may be prepared by the interaction of 5, 6, 7, 8-tetrahydro-2-methylisoquinolinium bromide and *p*-methoxy-benzyl magnesium bromide, when the former gets metathesized and the resulting product rearranges at the expense of the 1, 2-double bond. The said compound may be redrawn so as to show the subsequent reactions more vividly. The resulting product is dissolved in hydrochloric acid, hydrogenated at C_3 and C_4 with platinized charcoal and treated with ammonia to yield the corresponding *dl*-1, 2, 3, 4, 5, 6, 7, 8-octahydro derivative from which the *1*-enantiomorph is resolved by standard methods. The *1*-enantiomorph on

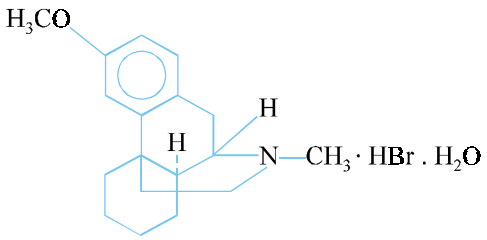
heating with phosphoric acid at 150° affords cyclization between the isoquinoline residue and the benzene ring at the expense of the lonely double bond existing in the isoquinoline nucleus. Conversion of the methoxy group to hydroxy usually takes place during heating with phosphoric acid earlier and the subsequent treatment with aqueous tartaric acid yields the official compound.



It is a potent narcotic analgesic having actions and structure similar to that of morphine. It is used effectively for the management of both moderate and severe pain. It produces significant analgesia at a dose level much lower than that of either **morphine** or **meperidine** and proves to be longer-acting than these drugs. *It is 2 to 3 times more potent than morphine*.

Dose : *Oral, severe pain 1.5 to 4.5 mg 1 or 2 times daily ; Subcutaneous, intramuscular, usual single dose 2 to 4 mg.*

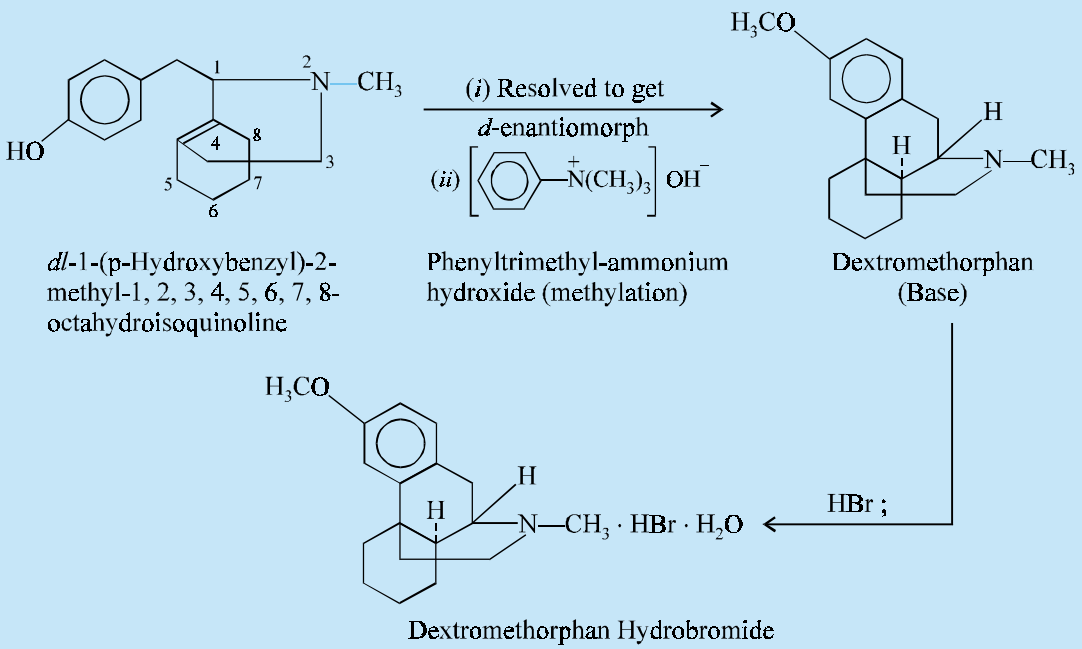
B. Dextromethorphan Hydrobromide BAN, USAN, Dextromethorphan INN,



3-Methoxy-17-methyl-9α, 13α, 14α-morphinan hydrobromide monohydrate ; Morphinan, 3-methoxy-17-methyl-, (9α, 13α, 14α)-, hydrobromide, mono-hydrate ; B.P., U.S.P.

Romilar(R) (Roche) ; Dormethan(R) (Dorsey) ; Benilyn DM(R) (Parke-Davis) ; Methorate(R) (Upjohn)

Synthesis

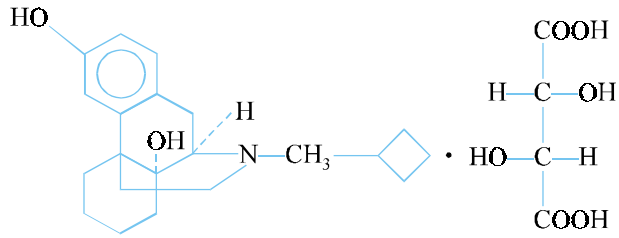


The racemic mixture (*dl*) of 1-(*p*-hydroxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydro-isoquinoline may be obtained exactly in the same manner as described for **levorphanol tartrate** (in 1 above). This is now resolved to get the *d*-enantiomorph and then treated with phenyltrimethyl ammonium hydroxide to cause methylation and yield the **dextromethorphan** base. Treatment of the base with appropriate amount of hydrobromide gives the corresponding hydrobromide.

It is a synthetic **morphine** derivative used as an antitussive agent exclusively. It has been reported to possess a cough suppression potency nearly one-half that of **codeine**. It exhibits no depression of the central nervous system, lacks analgesic actions and is free from addiction characteristics, which collectively render it possible for its use in cough syrups meant for infants and children.

Dose : *Usual, adult, oral, 10 to 30 mg 3 to 6 times a day ; not to exceed 60 to 120 mg in a day ; Children (6 to 12) : 2.5 to 5 mg 6 times a day, not to exceed 40 to 60 mg in a day ; Children (2 to 6) : 1.25 to 2.5 mg 3 to 4 times daily ; not to exceed 30 mg per day.*

C. Butorphanol Tartrate BAN, USAN, Butorphanol INN.



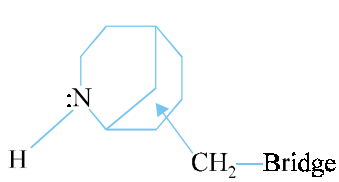
(-)-17-(Cyclobutylmethyl) morphinan-3, 14-diol D-(-)-tartrate (1 : 1) (salt) ; Morphinan-3, 14-diol, 17-(cyclobutylmethyl)-, (-)-, [S-(R^*, R^*)]-2, 3-dihydro-butanedioate (1 : 1) (salt) ; U.S.P., Stadol$^{(R)}$ (Bristol)

It is a synthetic opioid parenteral analgesic with actions and uses similar to those of **morphine**. It is usually employed *for the relief of moderate to severe post-surgical pain.*

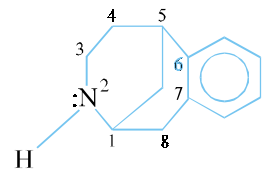
Dose : *Usual, adult, intramuscular, 2 mg 6 to 8 times a day ; usual, intravenous, 1 mg every 3 to 4 hours.*

4.3. Morphan Analogues

The morphan nucleus is nothing but a bridged perhydroazocine. The numbering pattern of benzomorphan, and the 6, 7-benzomorphan nomenclature has been adopted in the text.



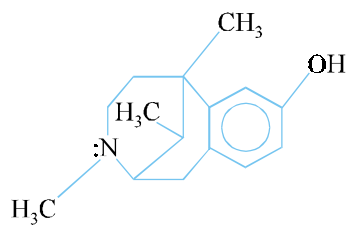
Bridged perhydroazocine



6, 7-Benzomorphan

A few members belonging to the morphan analogues are described here, *e.g.*, **metazocine ; cyclazocine ; pentazocine ;**

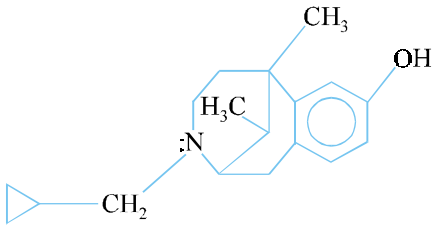
A. Metazocine INN, BAN, USAN,



2′-Hydroxy-2, 5, 9-trimethyl-6, 7-benzomorphan

It possesses analgesic activities but owing to its overwhelming psychotomimetic side-effects it is more or less unsuitable for use as an analgesic.

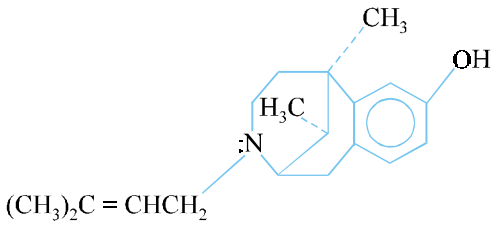
B. Cyclazocine INN, BAN, USAN,



3-(Cyclopropyl-methyl)-1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl-2, 6-methano-3-benzazocin-8-ol ; 2, 6-Methano-3-benzazocin-8-ol, 3-(cyclopropylmethyl)-1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl

It is a **benzomorphan analogue** about 40 times more potent than morphine as an analgesic and about 100 times more potent than nalorphine as an antagonist. The addiction potential of this drug seems to be much less than that of morphine. It has been used clinically to **treat diamorphine or morphine addicts.**

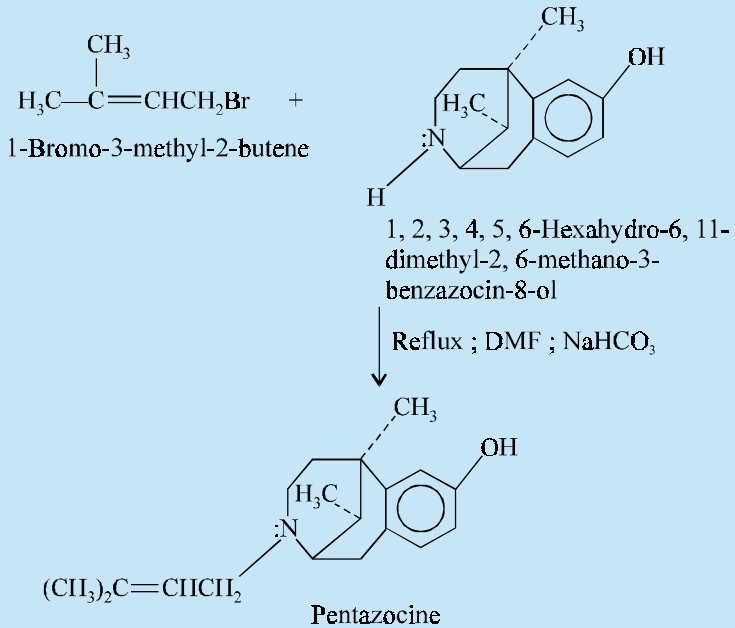
C. Pentazocine INN, BAN, USAN,



(2*R**, 6*R**, 11*R**)-1, 2, 3, 4, 5, 6-Hexahydro-6, 11-dimethyl-3-(3-methyl-2-butenyl)-2, 6-methano-3-benzazocin-8-ol ; 2, 6-Methano-3-benzazocin-8-ol, 1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl-3-(3-methyl-2-butenyl)-, (2α, 6α, 11R*)- ; B.P., U.S.P.,

Fortral(R) (Winthrop) ; Talwin(R) (Winthrop)

Synthesis



It may be prepared by the condensation of 1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl-2, 6-methano-3-benzazocin-8-ol with 1-bromo-3-methyl-2-butene by refluxing them together in dimethylformamide as a medium and in the presence of sodium bicarbonate. The crude pentazocine is extracted with an appropriate solvent and purified by recrystallization from aqueous methanol.

It is a synthetic analgesic agent commonly used *for the control of moderate to acute pain.* It exerts some sedative actions. It causes incomplete reversal of the respiratory, cardiovascular and behavioural depression produced by either **meperidine** or **morphine**.

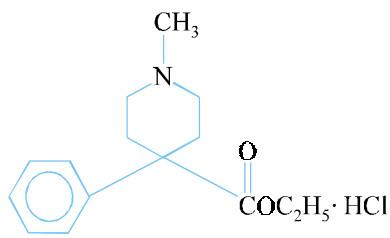
It behaves both as an agonist and as an antagonist. It is reported to be 3 to 4 times less potent than morphine and about 50 times less potent than nalorphine.

Dose : *Parenteral, 20 to 60 mg (as lactate) ; usual, 30 mg 6 to 8 times a day ; daily dose must not exceed 360 mg.*

4.4. 4-Phenylpiperidine Analogues

A spectacular accidental discovery of meperidine, in the course of search for structural analogues of atropine with a view to evolve anticholinergic drugs, proved to be a successful attempt towards the synthesis of 4-phenylpiperidine derivatives as narcotic analgesics. This finding has further strengthened the belief that the synthesis of relatively simpler components of the complex molecule of morphine may give rise to a more rational approach towards more efficacious analgesics having lesser nonaddictive liabilities. This ultimately led to the synthesis of a number of the following interesting compounds, namely : **pethidine hydrochloride ; diphenoxylate hydrochloride ; fentanyl citrate ; anileridine hydrochloride ; phenoperidine hydrochloride ;**

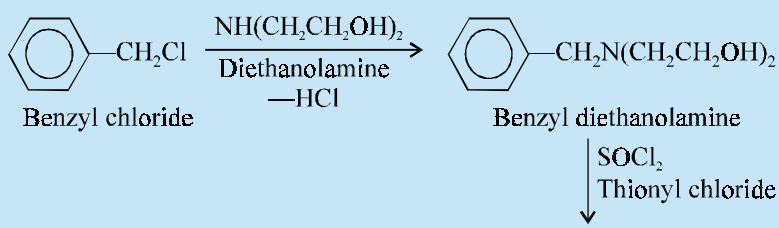
A. Pethidine Hydrochloride BAN, Meperidine Hydrochloride USAN, Pethidine INN,



4-Piperidinecarboxylic acid, 1-methyl-4-phenyl-, ethyl ester, hydrochloride ; Ethyl-1-methyl-4-phenyl-isonipecotate hydrochloride ; Pethidine Hydrochloride B.P., Eur. P., Int. P., Ind. P., Meperidine Hydrochloride U.S.P.,

Denerol(R) (Breon) ; Mepadin(R) (Merrell Dow)

Synthesis



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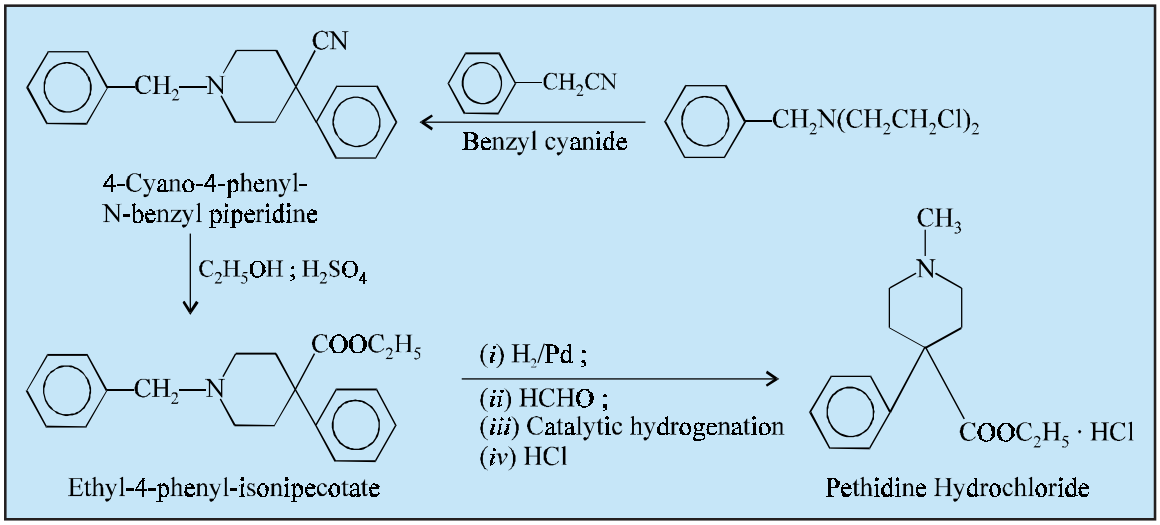
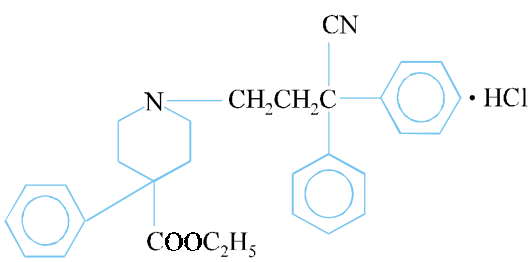


Benzyl diethanolamine is prepared by the interaction of benzyl chloride and diethanolamine with the elimination of a mole of HCl. Chlorination with thionyl chloride gives the corresponding chloride analogue which on treatment with benzyl cyanide yields 4-cyano-4-phenyl-N-benzyl piperidine. Esterification with ethanol in the persence of a small amount of concentrated sulphuric acid yields the ethyl ester. The N-benzyl group is removed by means of catalytic hydrogenation in acetic acid solution employing a palladium catalyst. Addition of formaldehyde to the reduction mixture followed by further catalytic hydrogenation yields **pethidine** which is finally converted to the hydrochloride by neutralization with hydrochloric acid.

It is a **synthetic narcotic analgesic** which possesses the action and uses of morphine and may be used **for the relief of a variety of moderate to severe pain including the pain of labour and post-operative pain. Pethidine has atropine-like action on smooth muscle.** It is normally used to induce both sedation and analgesia simultaneously.

Dose : *Parenteral, usual, adult, oral, 50 to 150 mg 6 to 8 times a day as necessary.*

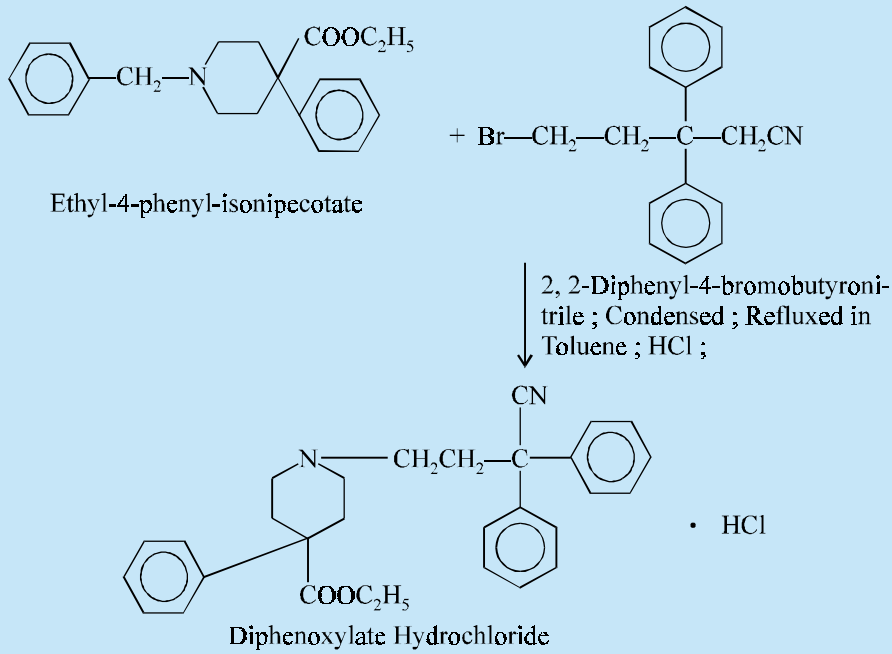
B. Diphenoxylate Hydrochloride BAN, USAN, Diphenoxylate INN,



Ethyl, 1-(3-cyano-3, 3-diphenylpropyl)-4-phenylisonipecotate monohydro-chloride ; 4-Piperidinecarboxylic acid, 1-(3-cyano-3, 3-diphenylpropyl)-4-phenyl-, ethyl ester, monohydro-chloride ; B.P., U.S.P.,

Component of Lomotil$^{(R)}$ (Searle)

Synthesis

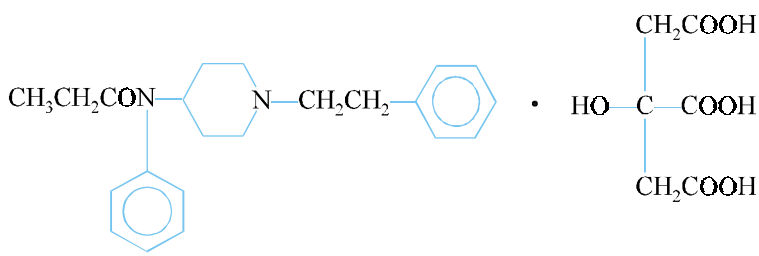


Ethyl-4-phenylisonipecotate is perpared as described above in pethidine hydrochloride, which is then condensed with 2, 2-diphenyl-4-bromobutyronitrile by refluxing together in toluene using an excess of the ester.

It is a synthetic analogue of **pethidine** with some analgesic activity but is mostly used in the *treatment of diarrhoea associated with gastroenteritis, irritable bowel, acute infections, hypermotility, ulcerative colitis and sometimes even food poisoning. It prevents hypergastrointestinal propulsion by reducing intestinal motility.*

Dose : *Usual, adult, oral 5, mg 4 times daily.*

C. Fentanyl Citrate BAN, USAN, Fentanyl INN,

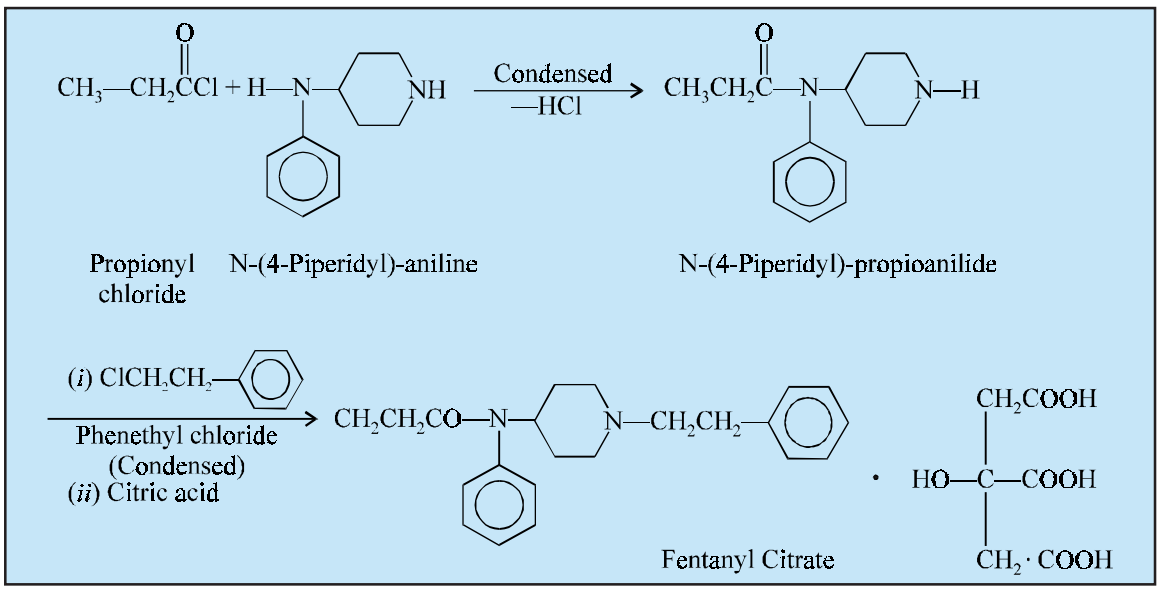


Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1, 2, 3-propanetricarboxylate (1 : 1) ; N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1 : 1) ; Phentanyl citrate ; B.P., U.S.P.,

Sublimaze(R) (Janssen).

Synthesis

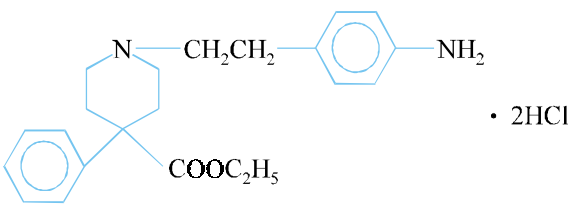
N-(4-Piperidyl) propioanilide is prepared by the condensation of propionyl chloride with N-(4-piperidyl)-aniline. The resulting product is further condensed with phenethyl chloride to obtain the corresponding fentanyl base which on reaction with an equimolar portion of citric acid gives rise to the (1 : 1) citrate.



It is a potent narcotic analgesic *primarily employed as an analgesic for the arrest of pain after all types of surgical procedures. It possesses an inherent rapid onset and short duration of action. It may be employed also as an adjuvant to all such drugs mostly used for regional and general anaesthesia.*

Dose : *Intramuscular, usual, in pre-operative medication 0.05 to to 0.1 mg 30 to 60 minutes before surgical treatment ; for rapid analgesic action, 0.05 to 0.1 mg intravenously.*

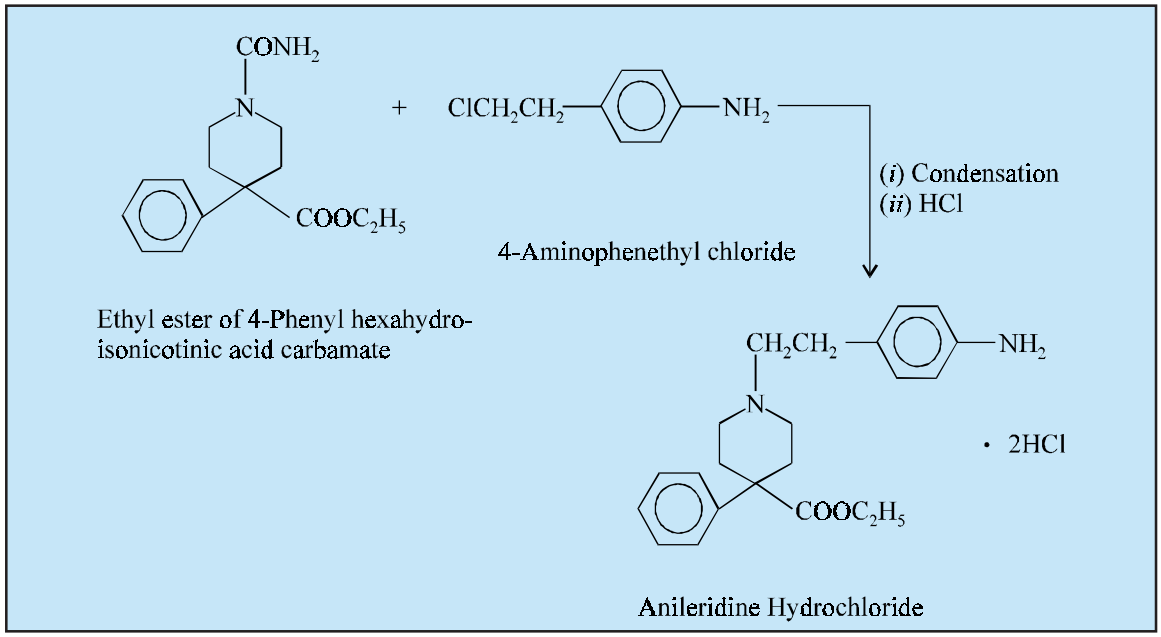
D. Anileridine Hydrochloride BAN, USAN, Anileridine INN,



4-Piperidinecarboxylic acid, 1-[2-(4-aminophenyl) ethyl]-4-phenyl-, ethyl ester, dihydrochloride ; Ethyl-1-(*p*-aminophenethyl)-4-phenylisonipecotate dihydrochloride ; U.S.P.

Synthesis

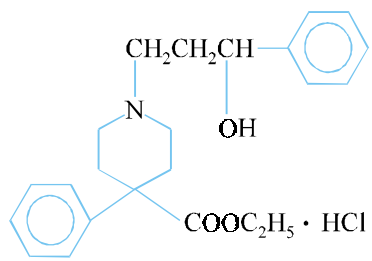
Anileridine hydrochloride is prepared by the condensation of the ethyl ester of 4-phenylhexahydroisonicotinic acid carbamate with 4-aminophenethyl chloride and subsequently treating the base with hydrochloric acid.



It is a narcotic analgesic having related chemical structure to that of pethidine and possesses an action similar to it, but with longer duration.

Dose : *Usual, oral, 25 mg every 6 hours.*

E. Phenoperidine Hydrochloride BAN, Phenoperidine INN, USAN,



1-(3-Hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester hydrochloride ; Ethyl 1-(3-hydroxy-3-phenyl-propyl)-4-phenylpiperidine-4-carboxylate hydrochloride ;

Operidine$^{(R)}$ (Janssen, U.K.)

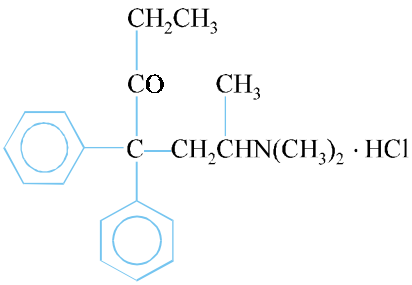
It is a potent analgesic with actions similar to morphine. It produces neurolepanalgesia, when administered with a major tranquillizer or neuroleptic agent like droperidol, that enables a patient to become calm and indifferent to his environment thereby offering the required co-operation with the surgeon.

Dose : *Average, initial, IV, for anaesthesia, 1 mg ; supplemented by 500 mcg every 40 to 60 minutes.*

4.5. Phenylpropylamine Analogues

Methadone, a repersentative of this class of compounds may have emerged purely from the molecular design and development of diphenylaminoethyl-propionates ior from the cleavage of piperidine ring present in pethidine molecule. These are considered to be the extremely flexible amongst most analgesic analogues *conformationally*. The following are a few classical examples of this group of analgesics, *viz.*, **methadone hydrochloride ; dextro-moramid tartrate ; dextropropoxyphene hydrochloride ; methotrimeprazine**

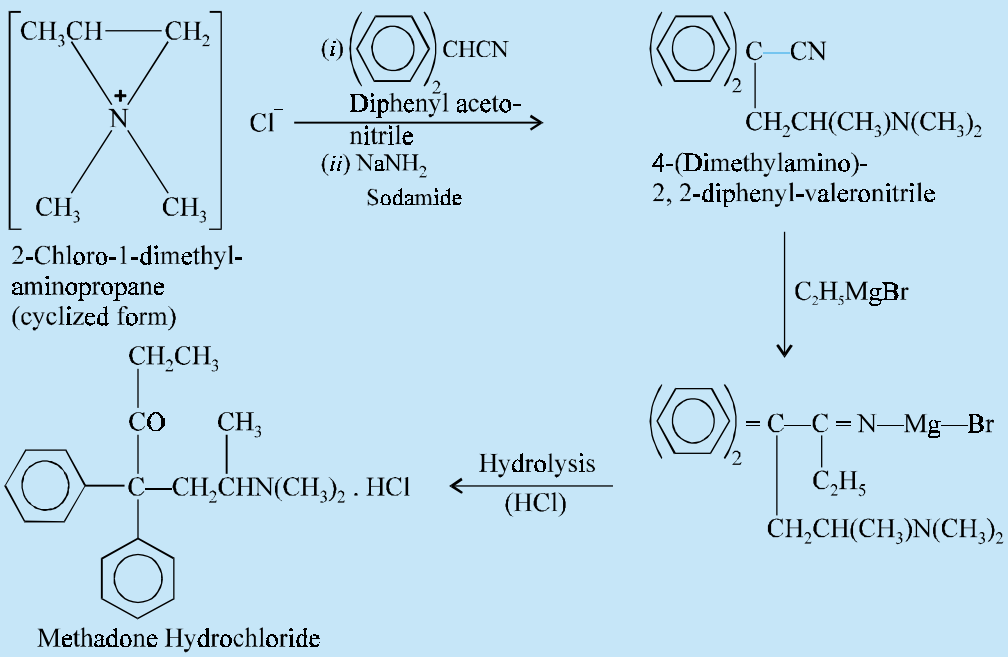
A. Methadone Hydrochloride BAN, USAN, Methadone INN,



6-(Dimethylamino)-4, 4-diphenyl-3-heptanone hydrochloride ; 3-Heptanone, 6-(dimethylamino)-4, 4-diphenyl-, hydrochloride ; Amidone Hydrochloride ; Phenadone ; B.P., U.S.P., Eur. P., Int. P., Ind. P.,

Dolophine Hydrochloride(R) (Lilly) ; Adanon Hydrochloride(R) (Winthrop)

Synthesis

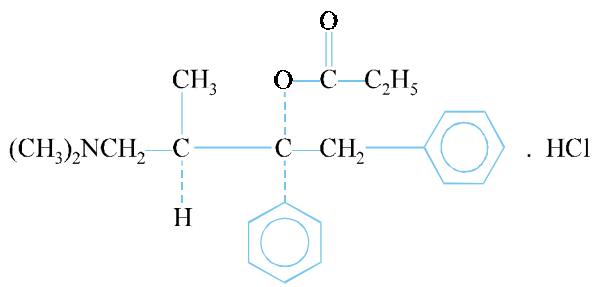


4-(Dimethylamino)-2, 2-diphenylvaleronitrile may be prepared by the condensation of the cyclized form of 2-chloro-1-dimethylaminopropane with diphenyl acetonitrile in the presence of sodamide; together with an undesired equimolar proportion of an isomeric nitrile. The undesired isomer is separated and rejected, while the right isomer is subjected to **Grignard Reaction** with ethyl magnesium bromide to yield an addition compound which on acidic hydrolysis forms the official compound.

It is a potent narcotic analgesics having actions quantitatively comparable to morphine though slightly less potent than morphine as an analgesic. Besides, it exerts sedation and antitussive properties. It also helps in the temporary maintenance and treatment of dependence on narcotic drugs, because its withdrawal syndrome has slow onset and much less intense than mrophine.

Dose : *Analgesic, oral, adult, im., 2.5 to 10 mg 6 to 8 times daily.*

B. Dextropropoxyphene Hydrochloride BAN, Propoxyphene Hydrochloride USAN, Dextropropoxyphene INN,



(2S, 3R)-(+)-4-(Dimethylamino)-3-methyl-1, 2-diphenyl-2-butanol propionate (ester) hydrochloride ; Benzeneethanol, α-[2-(dimethylamino)-1-methyl-ethyl]- α-phenyl-, propanoate (ester), hydrochloride, [S- (R^*, S^*)]- ; B.P., U.S.P.,

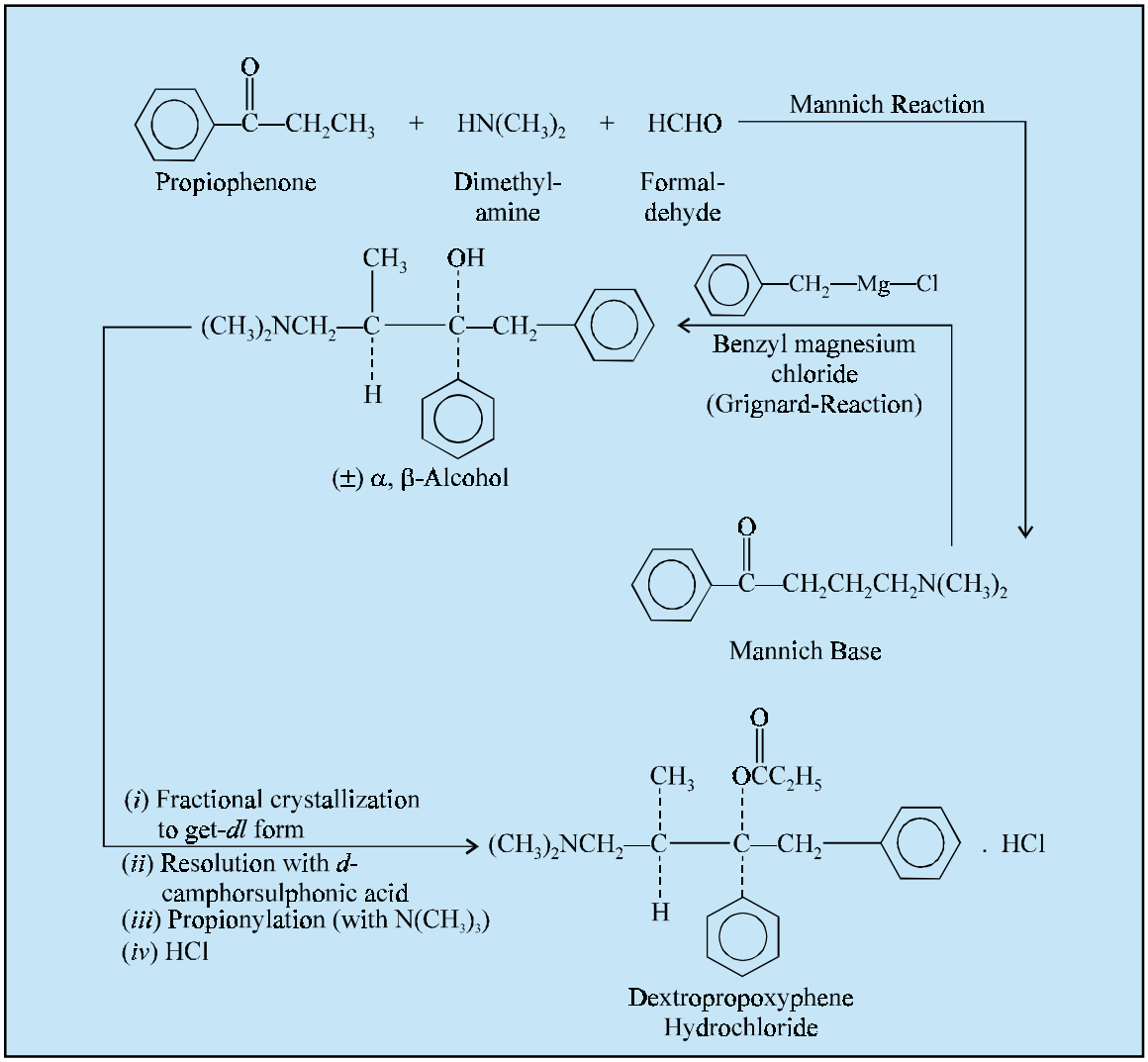
Darvon$^{(R)}$ (Lilly) ; SK 65$^{(R)}$ (SK & F) ; Dolene$^{(R)}$ (Lederle)

Synthesis :

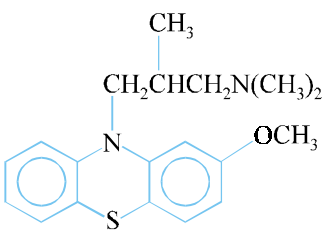
Interaction between propiophenone and dimethylamine in the presence of formaldehyde yields the Mannich base which is subjected to Grignardization with benzyl magnesium chloride to yield a racemic mixture of the two diastereoisomers designated as α- and β-alcohol. Fractional crystallization helps in the separation of α-*dl* form which is subsequently resolved by *d*-camphor-sulphonic acid to obtain (+)-α-form. This is now propionylated with propionic acid in the prsence of trimethylamine tio give dextropropoxyphene which takes up a mole of hydrochloric acid to form the desired official compound.

Dextropropoxyphene is a narcotic analgesic possessing relatively milder actions and bearing structural resemblance to methadone. **It is usually used to control mild to moderate pain and chiefly used along with other analgesics having anti-inflammatory and antipyertic properties like paracetamol and aspirin.**

Dose : *Usual, 65 mg, 3 or 4 times per day.*



C. Methotrimeprazine BAN, USAN, Levomepromazine INN,



(-)-10-[3-(Dimethylamino)-2-methylpropyl]-2-methoxy-phenothiazine ; 10H-Phenothiazine-10-propanamine, 2-methoxy-N, N, β-trimethyl-, (-)- ; B.P., U.S.P.,

Levoprome(R) (Lederle)

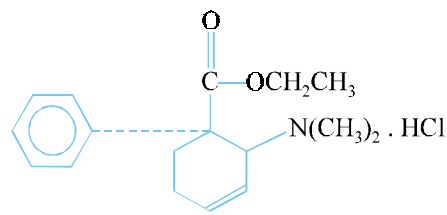
Methotrimeprazine possesses the histamine-antagonist characteristics of the antihistamines besides CNS effects comparable to those of chloropromazine. It exhibits significant analgesic properties and is *used in the management of severe chronic pain either alone or in conjunction with other analgesics.*

Dose : *Usual, adult, oral 25 to 50 mg per day for the treatment of mild psychoses and the severe psychoses 100 to 200 mg with a maximum up to 1 g daily.*

4.6. Miscellaneous Analogues

No discourse is usually given a touch of completeness unless and until the miscellaneous structures, which bear essentially the same pharmacological actions are grouped together. There are a few compounds that are analgesic but structurally do not belong to any of the earlier classified groups of compounds (A-E) :

A. Tilidate Hydrochloride BAN, Tilidine Hydrochloride USAN, Tilidine INN,



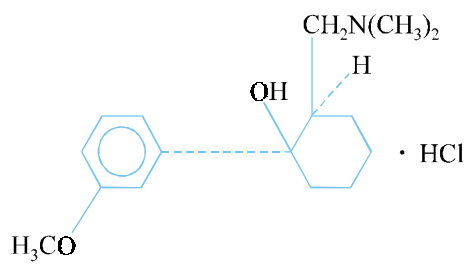
(±)-Ethyl *trans*-2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate hydrochloride ; 3-Cyclohexene-1-carboxylic acid, 2-(dimethylamino)-1-phenyl-, ethyl ester, hydrochloride (*trans*)-(±)- ;

Valoron(R) (Warner) ; Tilidine(R) (Parke-Davis)

It is a narcotic analgesic *mostly employed in the teratment of moderate to severe pain.*

Dose : *50 to 100 mg 4 times a day.*

B. Tramadol Hydrochloride BAN, USAN, Tramadol INN,



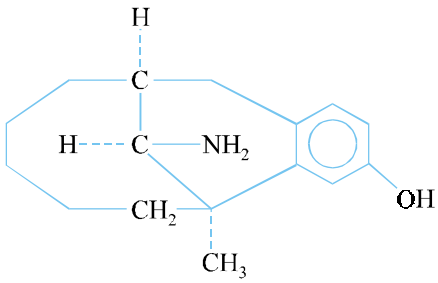
(±)-*trans*-2-[(Dimethylamino) methyl]-1-(*m*-methoxyphenyl) cyclohexanol hydrochloride ; Cyclohexanol, 2-[(dimethylamino) methyl]-1-(3-methoxy-phenyl)-, hydrochloride, *trans*-(±)- ;

Melanate(R) (Upjohn) ; Tramal(R) (Grunenthal, W. Ger.)

Tramadol is a potent narcotic analgesic.

Dose : *1 m or iv injection 50 to 100 mg ; as suppository 100 mg.*

C. Dezocine INN, BAN, USAN,



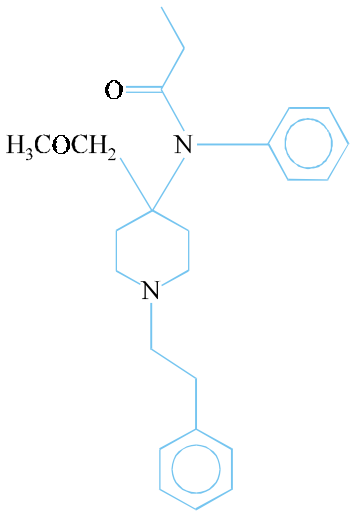
(-)-13 β-Amino-5, 6, 7, 8, 9, 10, 11α, 12-octahydro-5α-methyl-5, 11-methano-benzocyclodecen-3-ol ; 5-11-Methanobenzocyclodecen-3-ol, 13-amino-5, 6, 7, 8, 9, 10, 11, 12-octahydro-5-methyl-, (5α, 11α, 13S*)-, (-)- ;

Dalgan(R) (Wyeth).

Dezocine possesses analgesic as well as narcotic antagonist properties and is *usually administered by injection for the relief of severe pain.*

Dose : *10-15 mg.*

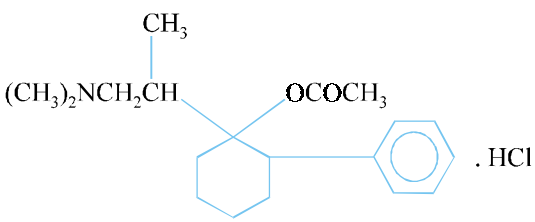
D. Sufentanil INN, BAN, USAN



N-[4-(Methoxymethyl)-1-[2-(2-thienyl) ethyl]-4-piperidyl] propionanilide ;

It is a narcotic analgesic.

E. Nexeridine Hydrochloride USAN, Nexeridine INN,



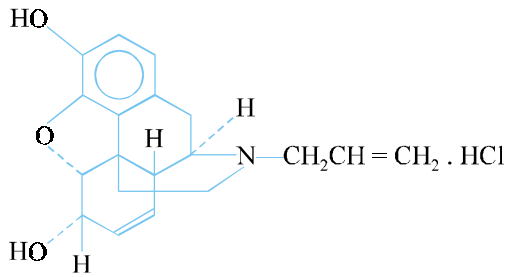
1-[2-(Dimethylamino)-1-methylethyl]-2-phenylcyclohexanol acetate (ester) hydrochloride ; Cyclohexanol, 1-[2-(dimethyl-amino)-1-methylethyl]-2 phenyl-, acetate (ester), hydrochloride.

Nexeridine is a narcotic analgesic.

5. NARCOTIC ANTAGONISTS

In 1915, it was shown that N-allylnorcodeine abolished both heroine- and morphine-induced respiratory depression. Almost 25 years later (1940), it was observed that N-allylnormorphine (commonly known as **nalorphine**) possessed more marked and significant morphine antagonizing actions. Thirteen years later (1953), it was demonstrated that nalorphine had the ability to *arrest severe abstinence syndromes in postaddicts* who were earlier treated briefly with either **morphine**, **methadone** or **heroine**. Examples of **narcotic antagonists** include : **nalorphine hydrochloride ; naloxone hydrochloride ; propiram fumarate and pentazocine**.

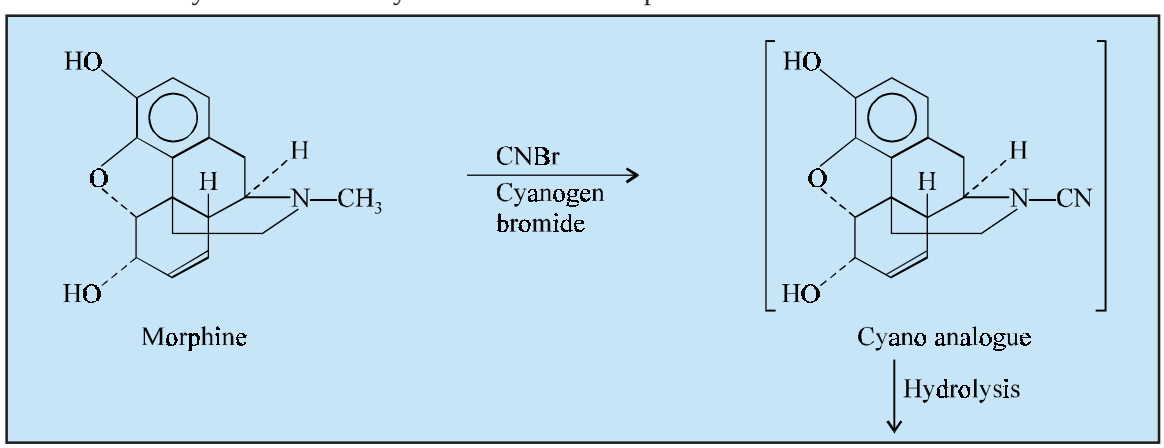
A. *Nalorphine Hydrochloride* BAN, USAN, *Nalorphine* INN,



17-Allyl-7, 8-didehydro-4, 5α-epoxymorphinan-3, 6α-diol hydrochloride ; Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-(2-propenyl)-(5α, 6α)-, hydrochloride ; U.S.P., Int. P., Ind. P., Nalline$^{(R)}$ (MS & D)

Synthesis

Morphine on treatment with cyanogen bromide gives the corresponding cyano analogue which upon hydrolysis forms the desmethylmorphine. This on reaction with allyl bromide and subsequent treatment with hydrochloric acids yields the official compound.



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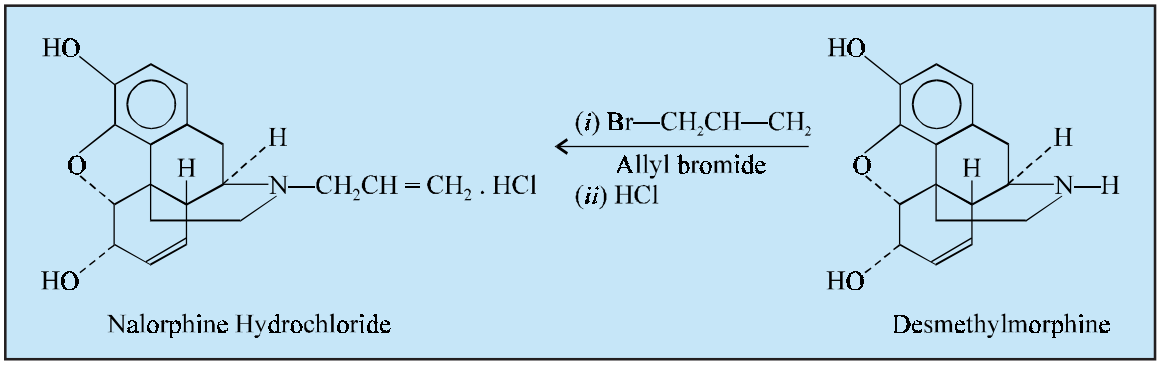
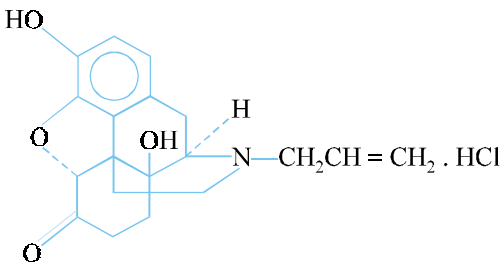


Nalorphine Hydrochloride — Desmethylmorphine

It is a narcotic antagonist having certain agonist actions that reduce the depressant actions particularly of **morphine** together with other narcotic drugs . It is pertinent to observe here that nalorphine does not exert its antagonistic effect caused by either barbiturates or other non-narcotic depressants. It possesses analgesic properties but is not used owing to its undesirable side-effects. **It is effectively employed to reverse narcotic-induced respiratory depression.**

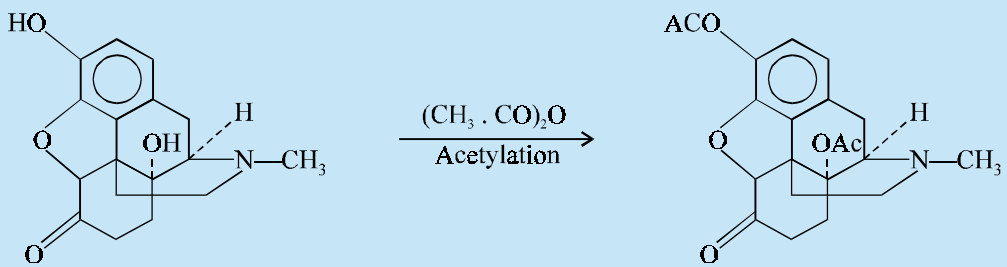
Dose : *Intravenous, 2 to 10 mg per dose ; usual, 5 mg repeated twice at 3 minute intervals if required.*

B. Naloxone Hydrochloride BAN, USAN, Naloxone INN,



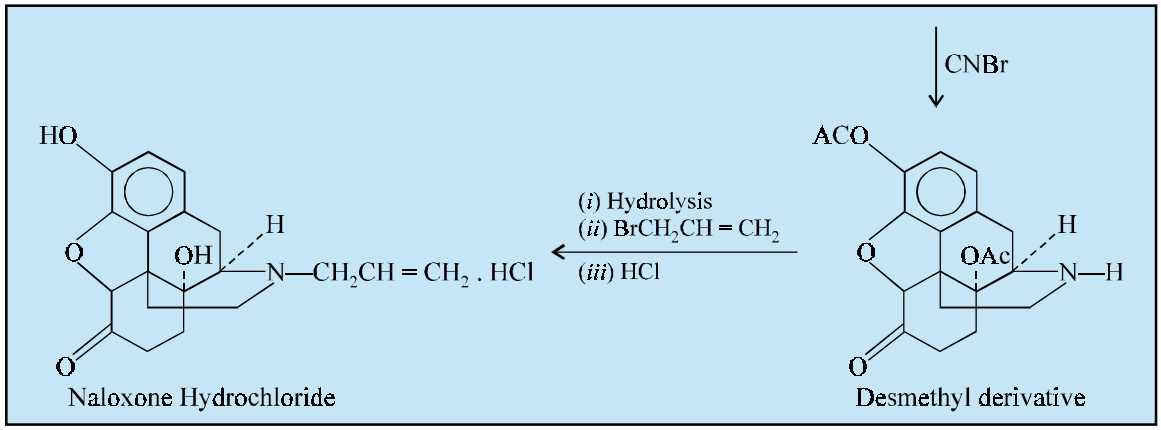
17-Allyl-4, 5α-3, 14-dihydroxymorphinan-6-one hydrochloride ; Morphinan-6-one, 4, 5-epoxy-3-[4-dihydroxy-17-(2-propenyl)-, hydrochloride, (5α)- ; (-)-N-Allyl-14-hydroxy-nordihydromorphinone hydrochloride ; Allylnoroxy-morphone Hydrochloride ; U.S.P., Narcan(R) (Endo)

Synthesis



Oxymorphone — 3, 6-Diacetate derivative

(*Contd...*)



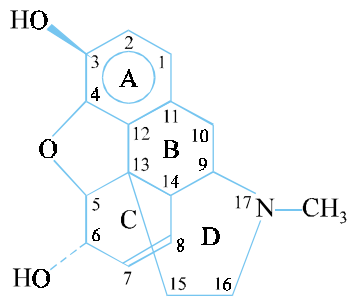
It may be prepared by the acetylation of **oxymorphone** to give 3, 6-diacetate derivative which on treatment with cyanogen bromide yields the desmethyl derivative.This on hydrolysis, followd by alkylation with allyl bromide and finally treating with hydrochloric acid forms the official compound.

Naloxone is a specific narcotic antagonist which, unlike nalorphine, possesses no morphine-like properties. It is considered to be an effective antagonist for mixed agonist-antagonist like pentazocine. It may also reverse some of the adverse effects of narcotic antagonists having agonist actions. **Owing to its lack of respiratory depressant property, it can be safely administered to patients suspected of narcotic overdosage without having the risk of further increasing respiratory depression. It has been found to reverse narcotic analgesic and possesses little analgesic properties of its own.**

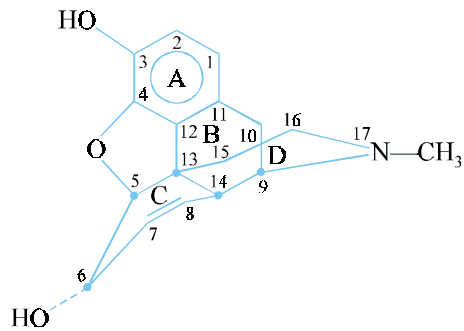
Dose : *Usual, parenteral, 0.4 mg (1 ml)*

6. MORPHINE : STRUCTURAL REPRESENTATIONS

In fact, the most probable structure of morphine was put forward in the year 1925 ; however, its confirmation by total synthesis was accomplished in 1955. Interestingly, the paucity of the knowledge with regard to the correct structure of **morphine,** nevertheless subsided the zeal and enthusiasm amongst the medicinal chemists to synthesize several morphine structural analogues by taking advantage of the various known chemical reactions with the peripheral functional moieties present in morphine, such as :



'*Flat*'-Representation
(A)



'*Steric*'-Representation
(B)

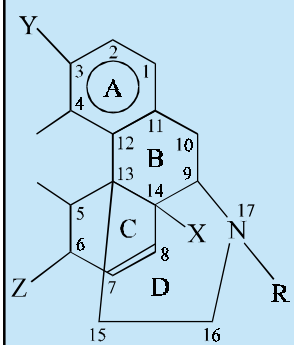
C-3 phenolic hydroxyl ; C-6 allylic alcohol ; and C = C between C-7 and C-8 as depicted in the following structure(s). It is, however, pertinent to mention here that several synthesized structural analogues even before 1930 are still constituted as vital and potential **'drugs'** in the therapeutic armamentarium, for instance : **codeine ; ethyl morphine** (*Dionin*$^{(R)}$) ; **diacetyl morphine** (heroin) ; **hydromorphone** (*Dilaudid*$^{(R)}$) ; **hydrocordone** (*Dicodid*$^{(R)}$) ; and **methyldihydromorphinone** (*Metopon*$^{(R)}$).

Morphine may be diagramatically represented as **'flat'** (A) configuration, and also as **'steric'** (B) configuration as illustrated above. Emphatically, in (B) the *ring* '*C*' essentially has the **'BOAT'**-conformation ; whereas the *ring*-'*D*' has the **'CHAIR'** conformation. Besides, the carbon atoms numbered 5, 6, 9, 13, and 14 (marked with a dark spot) are **chiral in nature** (*i.e.*, these are asymmetric C-atoms).

Morphine-related Antagonists and Agonists/Antagonists

The **National Research Council's Committee on Drug Addiction** established in the year 1929 under the leadership of Small LF (a chemist) and Eddie NB (a pharmacologist), synthesized a large number structural modifications of the **'morphine molecule'** with regard to its peripheral structural variants, intact morphine skeleton, and derivatives of compounds which could be considered as structural 'components' of the morphine molecule ; that ultimately gave rise to nearly **125 morphine analogues.** A comprehensive analgestic evaluation certainly helped in the emergence of emperical structure-activity relationships (SARs) as given in Table 11.2.

Table. 11.2 : Morphine-Related Antagonists and Agonists/Antagonists

General Structure	Name	R	X	Y	Z	Other	Therapeutic Category
	**Nalorphine**	—CH_2—CH = CH_2	H	OH	OH	—	Narcotic antagonist
	Levallorphan	—CH_2—CH = CH_2	H	OH	H	*a**	Narcotic antagonist
	Naloxone	—CH_2—CH = CH_2	OH	OH	=O	*b***	Narcotic antagonist
	Naltrexone	—CH_2— 	OH	OH	=O	*b*	Narcotic antagonist
	Nalbuphine	—CH_2— 	OH	OH	OH	*b*	Narcotic analgesic
	Butophanol	—CH_2— 	OH	OH	H	*a*, *b*	Narcotic analgesic

**a* = No *o-atom* between C_4 and C_5.

***b* = No *'double bond'* between C_7 and C_8.

7. MECHANISM OF ACTION OF CERTAIN NARCOTIC ANALGESICS

The mechanism of action of certain **'narcotic analgesics'** included in this chapter are discussed below :

7.1. Morphine Sulphate

Its most important action is on the brain more specifically its higher functions. It has been observed that an initial transitory stimulation is usually followed by a distinct depression of the brain, its higher functions, and above all its medullary centres. Besides, the spinal functions and reflexes are normally stimulated. Interestingly, it causes a visible change in perception in such a manner that the patient shows more to tolerance to pain and discomfort perhaps due to possible interference with '*pain conduction*'.

Because of its high addition potential and abuse, the 'drug' is classified as **Schedule II** drug under the **Controlled Substances Act.**

7.2. Codeine

Codeine is chiefly metabolized in the liver where it undergoes *o*-demethylation, N-demethylation and partial conjugation with glycuronic acid. It is mostly excreted in the urine as *narcodeine* and *morphine* (both as its free and conjugated form). It is found to be less apt than 'morphine' to produce nausea, vomitting, constipation and miosis. It also causes addiction liabilities resulting into enhanced tolerance limits.

Note. Naloxone is a '*specific antagonist*' in the situations arising from '*acute intoxication*'.

7.3. Hydromorphone Hydrochloride

It has less tendency to effect sleep than morphine when administered in equivalent analgetic doses. Therefore, the consequent relief from pain may be accomplished either without any sleep or stupefaction. It is a semi-synthetic analgetic, chemically and pharmacologically very much akin to morphine.

7.4. Hydrocodone Bitartrate (Dihydrocodeinone Bitartrate)

The pharmacological action is found to be lying almost midway between those of **codeine** and morphine. It has been observed that while on one hand it possesses more addition liability than **'codeine',** and on the other it displays absolutely very little evidence of its dependence or addiction with long-term administration.

Note. 'Tussionex$^{(R)}$—is an ion-exchange resin complex with it, that essentially releases the drug gradually in a sustained rate and is said to produce effective cough-suppression over a span of 10-12 hours.

7.5. Levorphanol Tartrate

It is a potent synthetic analgetic very much related chemically and pharmacologically to '*morphine*' ; and is invariably employed for the relief of acute pair. It is in many aspects closely related to morphine but its action is 6 to 8 times more potent. However, it has been observed that the gastro intestinal effects of this compound are appreciably on the lower range than those experienced with morphine. It is a narcotic with addiction liability quite akin to morphine ; therefore, almost same stringent precautions must be observed when prescribing this **'drug substance'** as for **morphine.**

7.6. Dextromethorphan Hydrobromide

Dextromethorphan is well absorbed from the GI-tract. It has been observed that the **'drug'** is largely metabolized in the liver ; and consequently, excreted through the urine either as *unchanged* **dextromethorphan** or as its **demethylated metabolites** including *dextorphan*, that interestingly possesses cough-depressant activity to a certain extent.

7.7. Butorphanol Tartrate

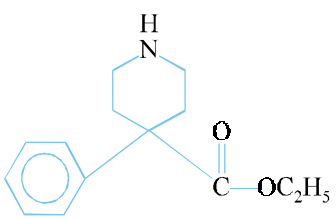
It is a potent synthetic opiate analgesic that gets completely absorbed from the GI tract after oral administration ; and, importantly, it undergoes almost 80% **first-pass metabolism.** It has been duly established that this '**drug**' enhances arterial resistance and the work of the heart (an action very much akin to **'petazocine'**) ; consequently, it is usually contra indicated in such patients who have a history of **acute myocardial infarction.**

7.8. Pentazocine

It happens to be a weak **'antagonist'** (1/30th than **'naloxone'**) at **mu receptors** ; and also acts as an **'agonist'** at **kappa receptors.** Its half-life after IM administration is 2.1 hour. It is found to exert weakly (nearly 1/50th than **'nalorphine'**) antagonizing effect on the analgesic effect produced by **morphine** and **meperidine**. Besides, it causes incomplete reversal of the cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. It also possesses certain degree of sedative action. The bioavailability of pentazocine after oral administration is only 20-50% due to the first pass metabolism. The **'drug'** gets metabolized extensively in the liver ; and subsequently, excreted by the urinary tract. It is, however, pertinent to mention here that the *two* major metabolites of **petazocine** are, namely : (*a*) *hydroxylation* of the *two* terminal methyl functional moieties attached to the N-substituent ; and (*b*) 3-*o*-conjugates, which are virtually **inactive**.

7.9. Meperidine Hydrochloride (Pethidine Hydrochloride)

The **'drug'** is largely metabolized in the liver with only a small quantum of it ~ 5% gets excreted unchanged. However, the short duration of action of meperidine is caused on account of its rapid metabolism *in vivo*. Importantly, the **'esterases'** predominantly cause cessation of the **ester linkage** (as ethyl ester at *para*-position) to leave as residue the **inactive-carboxylate analogue.** It also undergoes N-demethylation to yield the corresponding product known as **'normeperidine'**—a metabolite which gets accumulated after a prolonged medication with meperidine.



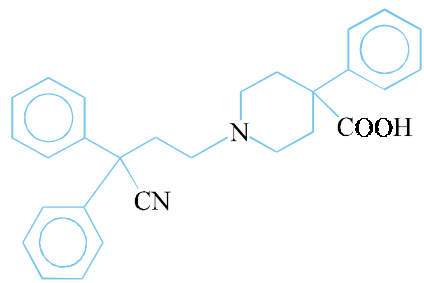
Normeperidine

Note. Normeperidine has only weak analgesic property, but it gives rise to sufficient CNS stimulation ; and it may end up grand mal seizures. Hence, it must be discontinued immediately in a subject showing the slightest symptoms of CNS stimulation apparently.

The elimination half-life of the **'drug'** is between 3-4 hours, but it may be simply doubled in patients with the liver malfunction. It has been observed that **'acidification'** of the urine may on one hand *increase the clearance of meperidine*, whereas on the other it may *retard the clearance of the toxic metabolite normeperidine.*

7.10. Diphenoxylate Hydrochloride

The '**drug**' itself possesses relatively low mu opioid agonist activity. It is, however, metabolized rather swiftly by means of ensuing *ester hydrolysis* to the corresponding **'free carboxylate'**, **difenoxin,** that exhibits 5 times more potent activity when administered orally. Interestingly, the inherent excessive higher polarity of difenoxin perhaps restricts its easier penetration into the CNS ; and, therefore, it provides an adequate explanation with regard to the comparatively **low abuse potential** of this narcotic analgesic.



Difenoxin

7.11. Fentanyl Citrate

It exhibits a profile of pharmacological action very much identical to morphine, and differs exceptionally on *two* accounts, namely : *first*-it does not cause emesis ; *secondly,* it does not release histamine. Its safety measure in frequency cases has not yet been fully understood. It is observed to cross the *placental barrier* ; therefore, its usage during labour may ultimately give rise to respiratory depression in the newly born infant. However, Fentanyl's transient action after the parenteral administration is caused solely on account of redistribution, rather than to '*metabolism*' or '*excretion*'. Hence, longer usage of this **'drug'** may cause in accumulation and toxicities.

Note. Recent advancement in its 'dosage forms' are :

(*a*) Fentanyl Transdermal Patch : It is used for the treatment of severe chronic pain, and it affords analgesia effictively for a duration ranging between 24—72 hours ; and

(*b*) Lollipop Dosage Form. It was introduced in the year 1999 for absorption from the buccal cavity (mouth).

7.12. Anileridine Hydrochloride

It is found to be more potent as compared to meperidine ; and, hence, possesses the same usefulness and limitations. Furthermore, its **'dependence capacity'**is significantly much lower ; and, therefore, it is well accepted as an appropriate and legitimate substitute for meperidine.

7.13. Phenoperidine Hydrochloride

It undergoes absorption from the GI-tract to a certain extent. It has been found that the **'drug'** gets extensively metabolized in the liver to **peltidine** and **norpeltidine**, that are subsequently excreted in the urine.

7.14. Methadone Hydrochloride

The cardinal activities of therapeutic value essentially comprise of : analgesia, sedation and detoxification or temporary maintenance in narcotic addiction. It has been observed that the '*drug*' is most rapidly absorbed (perhaps rather incompletely) after the oral administration, by virtue of the fact that only 52% of a given dosage gets discharged in urine. The mean plasma levels ranging between 182 to 420 mg. mL^{-1} are found in patients administered on a daily oral dose of 40 and 80 mg respectively ; of which 71 to 87% is in the '*bound form*'. Its biological half-life is nearly 25 hour, with a range of 13 to 47 hours.

Note. (1) It is one of the drugs of choice in the withdrawal management of patients addicted to morphine, heroin, and allied narcotic drugs.

(2) NALOXONE—is an effective '*antagonist*' in instances of acute intoxication.

(3) It is a '*Schedule II Drug*' under the *Controlled Substances Act* in US.

7.15. Propoxyphene Hydrochloride (Dextropropoxyphene Hydrochloride)

It is found, to be absorbed completely after oral administration ; however, **first-pass elimination** ranging between 30-70% reduces its **'bioavailability'** appreciably. The volume of distribution is 700 to 800 L ; oral clearance varies between 1.3 to 3.6 L. min^{-1} ; and the biological half-life is 6 to 12 hours. **Norpropoxyphene** happens to be the **'major metabolite'** having a half-life of 30-36 hours.

7.16. Methotrimeprazine (Levomepromazine)

A phenothiazine structural analogue, very intimately related to chlorpromazine, and exhibits extremely potent analgesic activity. Importantly, it is devoid of any dependence liability, besides it does not produce respiratory depression. It is specifically of **some extent of advantage** in such patients for whom **addiction** as well as **respiratory depression** are serious problems.

7.17. Tramadol Hydrochloride

The **'drug'** exhibits its a analgesic effect by categorically inhibiting the uptake of **norepenephrine** and **serotonin** which is believed to contribute to its analgesic effects. Its major metabolite is about 6 times more potent as an **analgesic ;** besides, it has 200 times greater affinity for the mu receptor.

7.18. Dezocine

It is a synthetic **opioid 'agonist'** *or* **'antagonist'** structurally akin to pentazocine, and having analgesic actions almost identical to morphine. Interestingly, it is a **'primary amine'** whereas the rest of the **'nonpeptide opioids'** are **'tertiary amines'.** Although, its exact receptor selectivity profile has not been reported so far, yet its pharmacological activities are quite similar to that of buprenorphine. It is observed to be a partial agonist at mu receptor sites, practically devoid of any effect at the kappa receptors ; and exhibits agonist effect at delta receptors to a certain extent.

Dezocine gets metabolized largely by glucuranidation of the phenolic hydroxy moiety and also by N-oxidation. Its metabolites are quite inactive, and gets excreted invariably through the renal passage.

7.19. Sufentanil

The introduction of the *para*-methoxymethyl moiety and the subsequent replacement of the bioisosteric phenyl group with a 2-thiophenyl into the **'fentanyl molecule'** give rise to a **10 times enhancement in the prevailing mu opioid activity**.

Hence, the resultant compound *i.e.*, **sufetanil** is found to exhibit higher potency to the extent of 600-800 times in comparison to morphine. When administered IV it gets metabolized rapidly having a biological half-life 2.4 hour. Its volume of distribution is 2.5 L kg^{-1}, 92.5% is bound to plasma protein ; and the plasma clearance is 0.8 L min^{-1}.

7.20. Nalorphine Hydrochloride

It has a **'direct antagonistic effect'** against **morphine, meperidine, methadone** and **levorphanol.** Interestingly, it does not show any antagonistic effect toward barbiturate or general anaesthetic depression. **Nalorphine** exerts its effect on the circulatory disturbances thereby reversing the effects of morphine. It is found to cause depression in the respiratory activity itself, that may potentiate the prevailing depression produced by **morphine.**

7.21. Naloxone Hydrochloride

It has been adequately proved based on the available evidence that naloxone specifically antagonizes the opioid effects, such as : respiratory depression, psychotomimetic effects, and pupillary constriction, by means of genuine competition for the receptor sites. The drug disappears from serum in man in a much rapid fashion. After an IV administration it is distributed quite rapidly in the body. It is found that the biological half-life in adults ranges between 30 to 81 minutes ; whereas, the mean half-life in neonates is 3.1 and 0.5 hour.

Naloxone is largely metabolized in the liver, primarily by glucuronide conjugation ; and ultimately excreted in the urine.

Note. Because of its short duration of action it is absolutely necessary to administer a multiple-dosing system that obviously limits its value.

Probable Questions for B. Pharm. Examinations

1. (*a*) What are narcotic analgesics ? Enumerate the **four**-serious limitations of these drugs.
(*b*) Give the structure, chemical name and uses of MORPHINE.
(*c*) What are the **three** important alkaloids isolated from *Papaver somniferum* ?

2. Classify narcotic analgesics by giving at least **one** typical example with its structure, chemical name and uses.

3. Discuss the **'morphine analogues'** and give the synthesis of :
(*a*) Diamorphine Hydrochloride and
(*b*) Hydrochloride Tartarate

4. Give the structure, chemical name and uses of any **two** important members of Morphinan Analogues. Discuss the synthesis of **one** of them.

5. Based on the **'morphan nucleus'** *i.e.*, a bridged perhyrozocine **three** drugs have been synthesized, namely : Metazocine, Cyclazocine and Pentazocine. Give their structure, chemical names and uses.

6. How would you synthesize **Pentazocine** from 1-bromo-3-methyl-2-butene ? Explain the route of synthesis.

7. The **4-phenylpiperidine analogue** led to the synthesis of much simpler compounds having potent analgesic properties. Discuss the synthesis of any **one** compound stated below :

(*a*) Meperidine hydrochloride and

(*b*) Fentanyl citrate

8. Give the names of any **two** important drugs based on **phenylpropylamine analogues** and describe the synthesis of **one** of them.

9. Discuss briefly Tilidate hydrochloride, Dazocine, catanlanil and Nexonine as **narcotic analgesics.**

10. Give a brief account of '**Narcotic Antagonists'.** Discuss Nalorphine hydrochlroide in details.

RECOMMENDED READINGS

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